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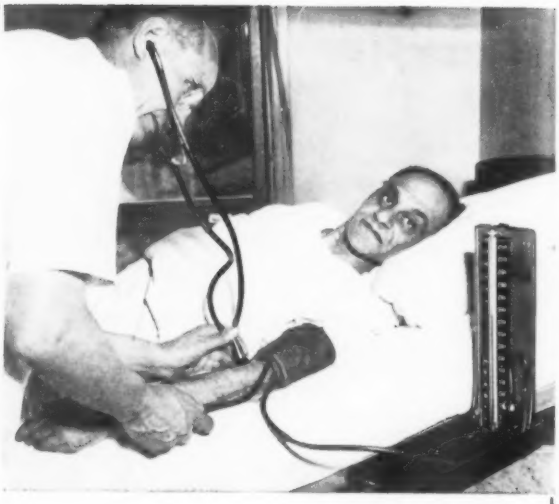

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THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

DECEMBER, 1951

ORIGINAL ARTICLES

FUNCTIONAL RESTORATION OF THE PARALYZED DIAPHRAGM FOLLOWING THE CROSS-UNION OF THE VAGUS AND PHRENIC NERVES*†

By JAMES O. BROWN, Ph.D.

AND

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RESPIRATORY muscular paralysis due to injury or disease may precipitate an acute and severe dyspnea. The chief interest of the afflicted individual focuses, naturally, upon the degree of functional recovery that may be achieved; yet some of these unfortunate and helpless individuals appear to be doomed to an "iron lung" existence.

If some way could be found to reestablish breathing in such individuals, an "iron lung" would be needed merely as a temporary expedient. Respiratory impairment due to diseased rather than killed anterior horn neurons will, in all probability, gradually diminish and the patient will return to a fairly normal existence as the recuperating neurons regain their former functional activity. In the case of neuronal death, however, nerve cell recovery is out of the question and permanent dependence upon a mechanical respirator threatens.

The phrenic nerve on each side connects the cervical spinal cord with the diaphragm; interruption of these nerves paralyzes this respiratory muscle. According to Sutton[6], the cells of the phrenic nerve are fairly frequently destroyed in humans when the cervical areas of the spinal cord are involved in poliomyelitis; and bilateral involvement with or without involvement of the intercostal muscles causes a respiratory disturbance resulting at times in death from asphyxia. To quote Wesselhoeft[9], "in complete and irreversible paralysis of the respiratory muscles, life can be maintained only by the use of the respirator".

The present report concerns preliminary studies of a method for restoring function and independent breathing movements to the paralyzed diaphragm

* These experiments were aided by a grant to one of us (J.O.B.) from the Ella Sachs Plotz Foundation.

† Read before the American Association of Anatomists, Detroit, Michigan, March 22, 1951.

by means of an intrathoracic cross-anastomosis of the vagus and phrenic nerves. Motives impelling a pursuit of this study were (1) to find a method for the re-innervation of the paralyzed diaphragm, and (2) to offer to individuals with a paralyzed diaphragm the opportunity for emancipation from an "iron lung" existence. Such a functional rehabilitation would be of inestimable value to any individual afflicted with the sequelae of an upper spinal poliomyelitis.

Materials and Methods. Twelve experimental and 6 control operations were performed on 8 dogs. Strict adherence to aseptic precautions was followed in all operations. Nembutal anesthesia was used.

Entrance into the chest cavity was gained through the fifth intercostal space, selected for convenience. The collapsed lung was gently retracted; the vagus and phrenic nerves were identified, then exposed by splitting the overlying pleura. The vagus nerve was mobilized along the middle third of its intrathoracic extent, then cut about ½ inch beyond its recurrent laryngeal branch to insure the elimination of all nerve fibers destined to supply the laryngeal muscles. The phrenic nerve, all contributing roots to which having combined into one main trunk above this intrathoracic level, was mobilized through most of its intrathoracic course, then cut about 2 inches craniad to the diaphragm. A portion of the phrenic nerve about 1 inch in length was cut away from its proximal stump, the free end of which was then ligated, doubled back upon itself and ligated again in an effort to prevent the possible regrowth of phrenic nerve fibers.

The proximal part of the divided vagus nerve was then joined end to end by means of 1 or 2 black silk sutures through the perineurium to the cut distal fragment of the phrenic nerve; in 1 animal the nerves were maintained end to end by means of an autologous plasma clot.

A chest catheter was inserted temporarily, 300,000 units of procaine penicillin G in aqueous solution were deposited in the thorax and the incision was closed. The lung was then re-expanded and the inlying tube withdrawn quickly. Healing was by first intention and without complication.

The animals, unanesthetized and manually supported in an upright position with their feet on the floor, were roentgenoscoped to observe diaphragmatic motility, the unoperated side serving in each instance as a standard of comparison.

Experiments. EXPERIMENT 1. (GIRL). *Operation 1.* The left phrenic nerve was transected about 2½ inches craniad to the left dome of the diaphragm; a portion of this nerve, 2 inches in length, was removed from the proximal stump which was then ligated. The left vagus nerve was divided ½ inch distal to its recurrent laryngeal branch. The proximal left vagus stump was united end to end with the distal fragment of the left phrenic nerve by means of two black silk sutures (#00000).

On the 145th postoperative day, roentgenoscopy of the unanesthetized dog held in an upright position revealed the relative movements of the domes of the diaphragm to be: right side ++++, left side ——. The animal survived.

Operation 2. Exploration was done to remove the suture site and specimens from the experimentally crossed nerves. Numerous firm adhesions were present and, apparently, were responsible for the immobility of the lung and diaphragm. The animal survived.

EXPERIMENT 2. (MAGGIE). *Operation 1.* The left phrenic nerve was transected about 2½ inches craniad to the left dome of the diaphragm, a portion of this nerve, 2 inches in length, was removed from the proximal stump which was then ligated. The left vagus nerve was divided ½ inch distal to its recurrent laryngeal branch. The proximal left vagus stump was joined end to end to the distal left phrenic fragment through the use of an autologous plasma clot as the sutural material.

On the 138th postoperative day, roentgenoscopy of the unanesthetized dog held in an upright position revealed the relative movements of the domes of the diaphragm to be: right side ++++, left side +++. The animal survived.

Operation 2. Exploration was done to remove the suture site and specimens from the experimentally crossed nerves. The animal survived.

EXPERIMENT 3. (JERRY). *Operation 1.* The same procedure was carried out as in experiment 1.

On the 138th postoperative day, roentgenoscopy of the unanesthetized dog held in an upright position revealed the relative movements of the domes of the diaphragm to be: right side ++++, left side ++. The animal survived.

Operation 2. This comprises experiment 11, detailed below.

EXPERIMENT 4 (BROWNIE). *Operation 1.* The same procedure was carried out as in experiment 1.

On the 131st postoperative day, roentgenoscopy of the unanesthetized dog held in an upright position revealed the relative movements of the dome of the diaphragm to be: right side ++++, left side ++. The animal survived.

Operation 2. This comprises experiment 13, detailed below.

EXPERIMENT 5 (QUEENIE). *Operation 1.* The same procedure was performed as in experiment 1.

On the 117th postoperative day, roentgenoscopy of the unanesthetized dog held in an upright position revealed the relative movements of the domes of the diaphragm to be: right side ++++, left side ++++. The animal survived.

Operation 2. This comprises experiment 10, detailed below.

EXPERIMENT 6 (PRINCESS). *Operation 1.* The same procedure was carried out as in experiment 1.

On the 96th postoperative day, roentgenoscopy of the unanesthetized dog held in an upright position revealed the relative movement of the domes of the diaphragm to be: right side ++++, left side +++. The animal survived.

Operation 2. This comprises experiment 7, detailed below.

EXPERIMENT 7 (PRINCESS). *Operation 2.* The right phrenic nerve was transected about 3 inches craniad to the right dome of the diaphragm; a portion of the nerve, 2 inches in length, was removed from the proximal stump which was then ligated. The right vagus nerve was divided just craniad to the root of the right lung. The proximal vagus nerve stump was joined end to end to the distal fragment of the phrenic nerve and secured by means of two black silk sutures (#0000) placed perineurally.

On the following day, roentgenoscopy of the unanesthetized dog held in an upright position revealed the relative movements of the domes of the diaphragm to be: right side ––––, left side ++++. The animal survived.

On the 15th postoperative day, roentgenoscopy of the unanesthetized dog held in an upright position revealed the relative movements of the domes of the diaphragm to be: right side +++, left side ++++. The animal survived.

EXPERIMENT 8 (SHORTY). *Operation 1.* A portion of the right phrenic nerve was removed and the proximal stump ligated.

On the 3rd postoperative day, roentgenoscopy of the unanesthetized dog held in an upright position revealed the relative movements of the domes of the diaphragm to be: right side ––––, left side ++++. The animal survived.

Operation 2. This comprises experiment 9, detailed below.

EXPERIMENT 9 (SHORTY). *Operation 2.* A portion of the left phrenic nerve was removed and the proximal stump ligated. This animal, now with both domes of the diaphragm paralyzed, lived only a few hours and died during the night.

EXPERIMENT 10 (QUEENIE). *Operation 2.* A portion of the right phrenic nerve was removed and the proximal stump of this nerve was ligated.

On the 3rd postoperative day, roentgenoscopy of the unanesthetized dog held in an upright position revealed the relative movement of the domes of the diaphragm to be: right side ––––, left side ++++. The animal survived.

EXPERIMENT 11 (JERRY). *Operation 2.* A portion of the right phrenic nerve was removed and the proximal stump of this nerve was ligated.

The following morning this animal was in a fight with another dog in the same enclosure and died as a result.

EXPERIMENT 12 (JASMINE). *Operations 1 and 2.* Parts were removed from both phrenic nerves; the proximal stump of each was ligated.

The animal failed to survive longer than 10 minutes postoperatively.

EXPERIMENT 13 (BROWNIE). *Operation 2.* A portion of the right phrenic nerve was removed and the proximal stump of this nerve was ligated.

On the 63rd postoperative day, roentgenoscopy of the unanesthetized dog held in an upright position revealed the relative movements of the domes of the diaphragm to be: right side ––––, left side +++. The animal survived.

EXPERIMENT 14 (QUEENIE). *Operation 3.* This procedure was confirmatory to the controls. The suture site (left side) was identified, then removed. Both domes of the diaphragm were now paralyzed, the right having been denervated in experiment 10. The predictable failure of this animal to survive substantiated the results of the controls.

EXPERIMENT 15 (BROWNIE). *Operation 3.* This procedure was confirmatory to the controls. The suture site (left side) was identified, then removed. Both domes of the diaphragm were now paralyzed, the right having been denervated in experiment 13. The predictable failure of this animal to survive substantiated the results of the controls.

Table 1 summarizes the number of experimental and control animals used in the foregoing experiments and the outcomes in terms of survival.

Results and Discussion. Regeneration has been achieved repeatedly among a variety of different nerves. Details concerning the various methods and techniques for suturing nerves are not of primary concern here; rather these may be secured from a wealth of literature already available covering this phase of study (see bibliography in Lyons and Woodhall[3]). A search of the literature, however, has failed to reveal any previous experiment involving the cross-anastomosis between the proximal stump of the vagus nerve and the distal fragment of the phrenic nerve.

TABLE 1. SUMMARY OF NUMBERS OF OPERATIONS PERFORMED UPON 8 DOGS AND RESULTS (SURVIVAL)

Total animals used	*Animals with experimental nerve unions*	*Control animals*	*Experimental operations performed*	*Animals surviving experimental operations*	*Control operations*	*Animals surviving control operations*
8	6	2	12	6(100%)	6	0(0%)

Interest in this preliminary report is focused upon the final functional outcome after opportunity has been given for vagal fibers to grow through the distal fragment of the phrenic nerve to the diaphragm to see whether or not the re-activation of this paralyzed effector structure could or would occur.

When both phrenic nerves in the dog are interrupted simultaneously, the animal dies within a relatively short period of time. The labored breathing of the accessory muscles of respiration cannot continue for very long, since neither the amplitude of contraction nor the stamina of these accessory muscles is adequate for optimal inflation of the lungs (experiments 9, 12, 14, 15).

Experimentally, the procedure of cross-anastomosing the vagus and phrenic nerves initially on one side (experiments 1 to 6) had 2 very distinct advantages. First, it permitted the animals to breathe with the nonparalyzed half of the diaphragm while nerve regeneration proceeded on the paralyzed side. It was found in these experiments that the dog, like the human being, suffered no disability when only one-half of the diaphragm was paralyzed due to interference with the homolateral phrenic nerve. For some time postoperatively, before the regenerating vagal fibers had reached the diaphragm, the latter appeared at rest and devoid of contractions. In the absence of any suitable mechanical device for producing artificial respirations in the dog and because bilateral phrenic paralysis was found to be incompatible with life in this animal, only one side at a time could be used experimentally (experiments 6 and 7).

Second, an evaluation of the amount of functional return to the previously paralyzed half of the diaphragm after allowing time for nerve regeneration was accomplished through direct roentgenoscopic observations, the normally functioning half serving as a standard for comparison. When both halves of the diaphragm displayed active and synchronous contraction once again, a relative difference in amplitude between the 2 sides was obvious

roentgenoscopically, in some instances; in others, little or no difference was noticeable. By means of a plus and minus method for rating the observable gross differences in amplitude, an estimation of the amount of functional return gained by the paralyzed side was recorded. The longest postoperative interval between the vagus-phrenic cross-anastomosis and roentgenoscopically observed functional restoration of the diaphragm was 138 days (MAGGIE) while the shortest was 15 days (PRINCESS).

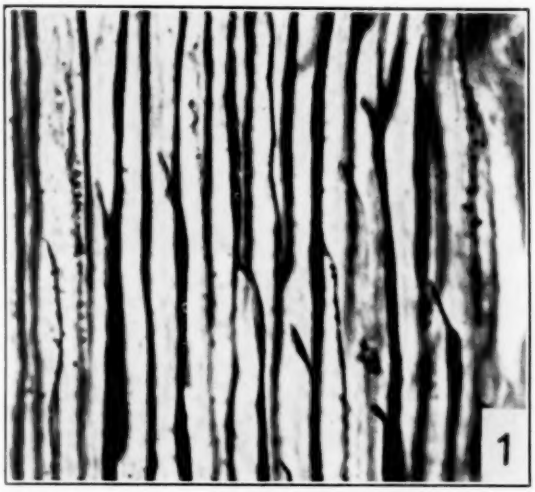

FIG. 1.—Normal phrenic nerve from an intrathoracic level between the root of the lung and the diaphragm on the left side. Note the predominance of large, heavily myelinated fibers. Control dog. X600.

Specimens of the experimentally crossed nerves removed subsequently from animals differing in postoperative intervals of time were studied morphologically. Nerve fibers from the proximal stump of the phrenic nerve were found neither grossly nor microscopically to have encroached upon the experimental suture site. For comparison, Fig. 1 shows normal phrenic nerve fibers; Figs. 2 to 6 portray the fine-gauged regenerating vagus nerve fibers, characteristic of regrowth in this peripheral nerve, coursing through the distal fragment of the phrenic nerve. Typical of the density attained by these small-diametered, regrown vagal fibers is that shown in cross section in Fig. 4.

Interruption of the phrenic nerve not followed by regeneration would result in some observable aspects of muscular atrophy of the diaphragm within the length of time following the phrenicotomy of these experiments. Under the influence of the regenerated fibers of the vagus nerve, muscular atrophy was prevented and the striated muscle appeared normal in every way (Figs. 4 to 6).

Over and above the observed return of function to the paralyzed half of the diaphragm and the existence, morphologically, of regrown vagal fibers, additional proof of diaphragmatic reinnervation was sought. As a further test of benefit, the most critical of all procedures was performed to deter-

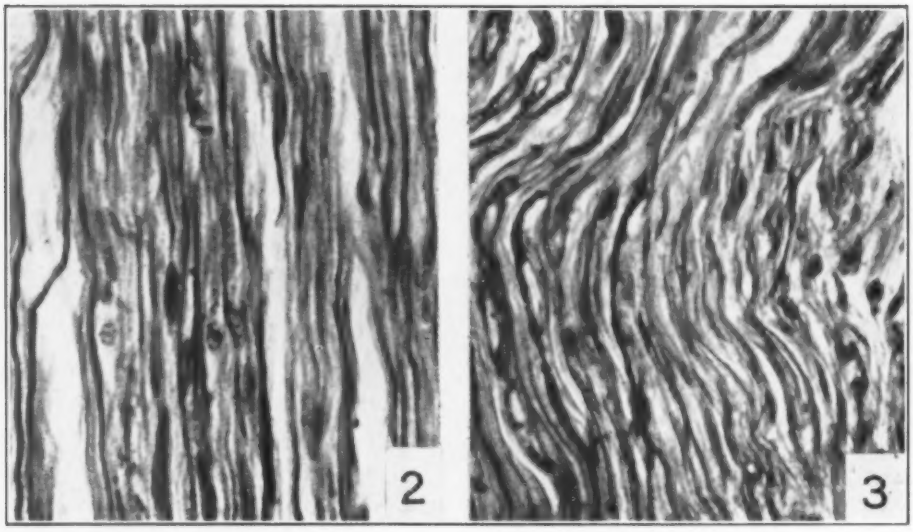

FIG. 2.—Regenerating vagus nerve fibers in the distal stump of the phrenic nerve near the suture site on the left side. Note the predominance of the fine fibers characteristic of regenerating nerves. Dog No. 5. X600.

FIG. 3.—Regenerating vagus nerve fibers in the distal stump of the phrenic nerve close to the left dome of the diaphragm. Note the abundance of the fine growing fibers. Dog No. 6. X600.

(All sections were stained with activated Protargol. The photomicrographs were taken by Mr. A. Marfaing to whom an expression of sincere gratitude is due.)

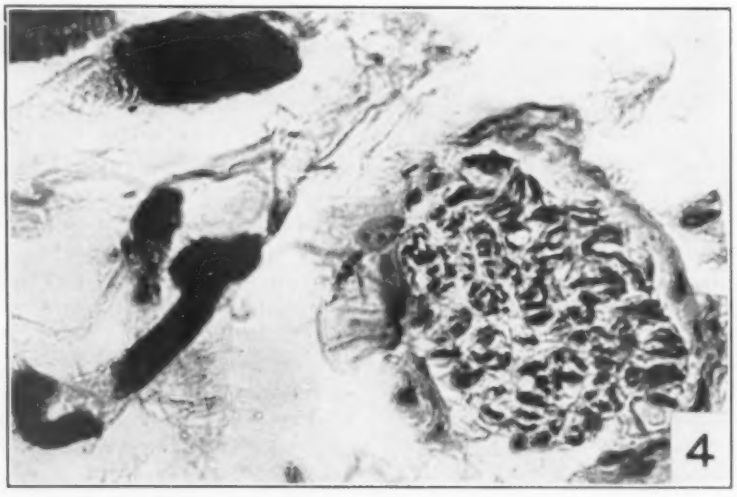

FIG. 2.—4. Section through the diaphragm close to its junction with the phrenic nerve. Note the cross-section of a small interfascicular ramus of the phrenic nerve on the left side now well populated with regenerated vagal fibers. Dog No. 6. X600.

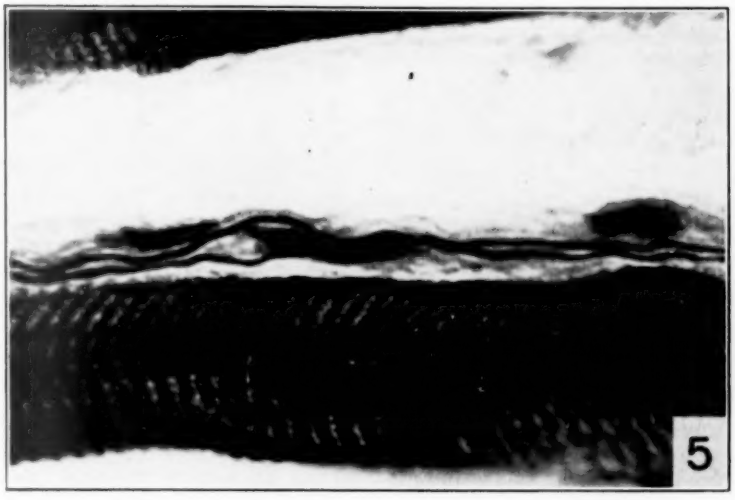

FIG. 5.—Section through the diaphragm showing 2 fine calibered regenerated vagal fiber branches extending between voluntary muscle fibers. Left side. Dog No. 6. X1200.

FIG. 6.—Section through the diaphragm showing the branching observed to occur along some of the re-grown vagal fibers. By this means, two or more muscle fibers may receive their nerve supply from single fibers of regenerating nerves. Left side. Dog No. 9. X1200.

mine whether or not the functioning experimentally crossed nerves were in reality independently able to innervate the diaphragm adequately for the respiratory demands of the individual. As noted above, each of the controls in experiments 9 and 12 succumbed quickly to a simultaneous, bilateral phrenicotomy. In view of this, then, division of the right phrenic nerves in animals possessing cross-anastomosed vagus and phrenic nerves on the left side (experiments 2 to 6) should produce complete diaphragmatic paralysis and death unless the regenerated vagal fibers through the experimental nerve crossing were innervating the muscle. All of these animals survived following the division of the right phrenic nerves (experiments 7, 10, 11, 13), substantiating beyond any doubt the functional restoration of the paralyzed diaphragm due to the regenerated vagal fibers. These findings ruled out conclusively, also, the possibility of re-innervating the paralyzed side of the diaphragm through what Edds[1] has called "compensatory branching of intact axons from the opposite side". Survival of these animals demonstrated the ability of the experimental side to contract independently.

When the suture site was removed in each of 2 animals (experiments 14, 15) in which the right phrenic nerve had been interrupted between 4 and 5 months previously, breathing having been sustained by the experimentally re-innervated half of the diaphragm, the animals succumbed in 10 minutes and served to confirm (and predictably so) the controls.

That the parasympathetic preganglionic component of the vagus nerve possesses the faculty to regenerate, was first proved definitely by Tuckett[7], who found that a cut vagus nerve in rabbits would in time regenerate and recover its function "even to cardiac and non-striated muscle."

The ability of the parasympathetic preganglionic fibers to regenerate into a voluntary motor nerve, however, and to make a functional connection with skeletal muscle ordinarily innervated by a somatic nerve has not been conclusively demonstrated by the experiments of others. We are now able to report that this can be accomplished through the cross-anastomosis of the vagus nerve, proximally, and the phrenic nerve, distally, an experiment never before performed to the best of our knowledge.

The rhythmic discharges of the vagus nerve provided a poor substitute for the useful rehabilitation of the dog's tongue in Schiff's[4] experiments. In order for the vagus nerve to re-innervate effectively the glossal musculature so that it may again perform its useful activity, the central connections of the vagus nerve would have to be altered considerably. Experimental results prove that no alteration of central connections occurs to correspond with altered peripheral connections (Sperry[5]). For this reason, the attempts by Langley and Anderson[2] to re-innervate successfully the diaphragm (from the standpoint of usefulness) by way of the cervical sympathetics met with failure because of the inability of the central connections of the sympathetic fibers to re-adapt to different circumstances of peripheral function. Impulses already being discharged rhythmically and automatically through the vagus nerve, therefore, make it an ideal substitute nerve for diaphragmatic re-innervation requiring no modification or change in the central connections of the vagal fibers. Our experiments on dogs have demonstrated this to be true.

The close inter-relationship between the respiratory and vagal centers and the influence of their functions upon each other has been brought out by Weiland, Burbacher, and Keiser[8].

These investigators have found that after bulbar involvement in poliomyelitis a loss of vagal function markedly affected the closely associated respiratory center, causing a pronounced slowing and irregularity of the respiratory rate. The influence exerted by the vagal center over the respiratory center was conspicuous by its absence in this case. When both the respiratory and vagal centers were involved, not only the rate and rhythm, but also the depth of the respirations was affected. The respirations became irregular and shallow. An undamaged and functional vagal center, therefore, exerts considerable influence over respiratory processes. When the outflow of impulses from the respiratory center becomes interrupted for any reason whatsoever, whether it be due to destruction within the center itself or to a lesion in the phrenic nerve, diaphragmatic paralysis ensues. Vagal influences conducted directly to the paralyzed diaphragm through the vagus–phrenic anastomosis restores activity once again to this important muscle of respiration in the dog.

The results of our experiments on dogs give more than a reasonable assurance that similar procedures can be duplicated in a practical way in humans, provided, of course, that atrophic changes in muscle due to long standing paralysis have not advanced beyond all chance for recovery.

Summary. 1. Paralysis of one-half of the diaphragm is not fatal in the dog.

2. Simultaneous paralysis of both halves of the diaphragm in the dog is fatal within 16 hours.

3. Intrathoracic unilateral vagotomy distal to the recurrent laryngeal nerve produces no observable disturbances in the dog.

4. In the absence of special treatment (namely, gastric fistula, regular lavage, esophagotomy, and others), intrathoracic bilateral vagotomy distal to the recurrent laryngeal nerves is fatal to the dog in less than 30 days.

5. Regeneration of parasympathetic preganglionic vagal fibers (that is, visceral efferent fibers) into the distal fragment of the phrenic nerve (somatic motor nerve) of the dog has been accomplished for the first time.

6. Preganglionic vagal fibers re-innervated the paralyzed diaphragm in the dog.

7. The re-innervated diaphragm in the dog contracted actively, rhythmically and automatically.

8. The re-innervated half of the diaphragm, restored once again to a useful function, was alone capable of maintaining breathing movements compatible with the active life of the dog, even after the opposite half of the diaphragm had been rendered nonfunctional.

9. The rhythmic impulses transmitted through the preganglionic vagal fibers served as a satisfactory substitute nerve for diaphragmatic re-innervation in the dog following a cessation of phrenic nerve impulses.

10. Because the preganglionic vagal fibers normally transmit rhythmic impulses, the functional outcome in the dog suggests that the central connections of these fibers are not altered or modified when they assume their new rôle in diaphragmatic innervation.

11. The practical application of this study to selected cases of human beings damaged by poliomyelitis is obvious.

Many thanks go to Doctors Serber and Tolsky in the Department of Roentgenology in Mount Sinai Hospital for helpful interpretations during the numerous roentgenoscopic examinations and to Doctor David Meranze, Director of Laboratories, Mount Sinai Hospital, and to Dr. George A. Bennett, Dean of the Jefferson Medical College and Director of the Daniel Baugh Institute of Anatomy in the Jefferson Medical College, for their many kindnesses.

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CONFUSION BETWEEN ACUTE MYOCARDIAL INFARCTION AND ACUTE PULMONARY EMBOLISM, CLARIFIED BY AUTOPSY MONTHS AFTER DEATH: AN IMPORTANT MEDICO-LEGAL PROBLEM

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The differential diagnosis between acute coronary thrombosis with myocardial infarction and acute pulmonary embolism at times is quite difficult. Errors in either direction may be made even under expert and most careful observation. Electrocardiograms, when very distinctive, may afford convincing evidence for myocardial infarction on the one hand or reveal changes that are very suggestive of acute cor pulmonale on the other[2]. The latter changes in the electrocardiogram often simulate to a great extent those seen in acute posterior myocardial infarction. However, there are many instances in which the electrocardiograms do not display characteristic changes of either condition, when one or the other is present. It is not the purpose of this communication to discuss the details of the differential diagnosis of these two entities but rather to emphasize a unique medico-legal problem and how it was solved.

Several years ago, two almost identical experiences occurred which we thought important enough to report to the medical profession. In the first instance, a lawyer wrote one of us to help in litigation concerning a death from coronary thrombosis which followed an accident. Not desiring to appear in court, the writer sent a reply that a written opinion would be given concerning the matter but that he did not wish to become involved to the extent of appearing in the courtroom. The details of the case were therefore forwarded to him for his opinion. The essence of the question put by the attorney was, "whether or not the injuries received by the patient either caused the coronary thrombosis or aggravated a previous arterial condition so as to cause the thrombosis." In a word, a healthy 37-year old man fractured his ankle which was put into a cast, and 4 weeks later he developed "indigestion pain" in the upper epigastrium, followed by death within a week. The diagnosis of coronary thrombosis was made by the attending physician and this was "confirmed" by electrocardiograms (See Case 1).

Case Reports. Case 1. C. M., a 37-year old pipe fitter, fell from a ladder and injured his left ankle on March 15th, 1945. He had been previously well and active, and able to do strenuous work and had never shown any signs or symptoms of coronary disease. After the above accident he tried to work for 14 days, hobbling around with the injured ankle. He was kept at a hospital, the ankle was strapped, legs were elevated, and hot packs were applied. The temperature, pulse, and respiration were normal. On April 5th, a cast was applied and the following day he was discharged from the hospital. At home he continued to have pain in his leg. On April

15th, he had pain in the upper abdomen and 2 days later the pain became severe and he collapsed. He was given morphine, atropine, papaverine, aminophylline, and oxygen. The diagnosis made by the physician was coronary thrombosis. The patient and his wife thought that he had "indigestion," the distress being just below the ensiform. On April 18th, a low-grade fever developed, and an electrocardiogram taken on April 19th was interpreted as "sinus tachycardia; coronary thrombosis: anterior type, and left axis deviation." On April 22nd, he rapidly grew worse and died; the cause of death stated on the death certificate was coronary thrombosis. No postmortem examination was performed.

Our first contact with this case was about 2 months after death. The important point involved was whether the widow could legally obtain compensation for the death of her husband from a coronary thrombosis taking place 4 to 5 weeks after the injury to the ankle. The following was part of the report sent to the attorney:

"Although there is much in the story that points to a coronary occlusion, I am by no means convinced that this is what happened. It is impossible for me to state with any degree of assurance concerning this. The reason for this doubt is that a pulmonary embolism could explain a good deal of what occurred. Firstly, this is a common complication after a fracture, in fact much more common than is a coronary thrombosis. Secondly, the electrocardiograms are as much in accord with an acute cor pulmonale from a pulmonary embolism as with a coronary thrombosis. Finally, the thoracic complication occurred at the right time for a pulmonary embolism. One, 2, or 3 weeks after a cast is applied to the leg for a fracture is the frequent time for developing a thrombophlebitis of the leg, which so often leads to a pulmonary embolism. The only way one could settle this question is by a postmortem examination. If this was not done previously, it might still be done in order to establish a correct diagnosis. If the correct diagnosis is acute pulmonary embolism, his death was directly caused by the accident. If he had an acute coronary thrombosis, the relationship between cause and death is not so close or certain. It is then debatable as to whether or not there is any relationship and I know of no way of dogmatizing on the subject."

Acting on the suggestion that was made, the attorney had the body disinterred and a postmortem examination was performed on July 5, 1945. Despite the fact that the body was examined 2½ months after death, 2 definite areas of infarction were found in the left lung. A large, laminated, brown thrombus of a friable nature occluded the pulmonary artery with extension of the thrombus into each main pulmonary branch, which on microscopic examination showed characteristics of an antemortem clot. The right side of the heart was dilated. The coronary arteries were essentially normal and so were the lumina of the vessels. A section taken through the anterior descending branch of the left coronary artery was normal. The valves of the heart, endocardium, myocardium, pericardium, and the aorta were normal. The iliac veins contained fluid blood. In the left femoral vein there was a thrombus which was firmly adherent to the vessel wall. It began at a point 20 cm. below the bifurcation of the profunda and the superficial branch, and extended to the knee. In the tibial vein there was also a thrombus from just above the ankle to the popliteal vein. The malleolus of the left tibia was fractured. Microscopic examination revealed the presence of early organization within the thrombus indicating that the clot was of some days' duration preceding death. The anatomical diagnosis was pulmonary embolism, pulmonary infarct (left lung), thrombosis of the left femoral and left tibial veins, and fracture of the medial malleolus of the left tibia.

From the medicolegal point of view the problem was readily and equitably solved after obtaining the above postmortem data. The widow obtained just compensation for the death of her husband which was then regarded as directly due to the accident.

Not many months after this experience, a somewhat similar request was made by an attorney in Columbia, Missouri. In this case the question was asked whether the prolonged mental and physical suffering which resulted from an accident could be held responsible for a fatal coronary thrombosis which occurred 7 months after the accident.

In brief, a 45-year old engineer who previously had been quite well and "never had a sick day in his life" suffered a crushing injury to his right foot on November 19, 1946. He had 2 surgical procedures performed, but throughout the subsequent months he suffered a great deal of pain in his foot

and limb. He was distressed nervously and physically because of the protracted illness and the loss of weight and strength. On June 18th, 1947, he had sudden pain in his chest which was diagnosed by his physician as coronary thrombosis. Some hours before he died, an electrocardiogram was taken which was diagnosed as "acute anterior infarction" (Fig. 1). He died on the following day, that is June 19th, 1947. The body was embalmed and no autopsy was performed (See case 2).

Case 2. G. E. P., a 45-year old man, suffered an injury to his right foot and ankle on November 19th, 1946. The foot was badly crushed by the fall of a heavy rock upon it and the distal end of the right tibia was fractured. The leg was immobilized in plaster for a short time prior to an ankle arthrodesis which was performed on December 4, 1946. He suffered considerable pain during the subsequent months. He was confined to bed for about 5 months during which period he deteriorated physically and nervously. The cast was removed on February 21st, 1947. The last 2 months of his life he got around on crutches but was in wretched condition. On June 18th, 1947, he developed pain in his chest and died the next day. He had been distressed and worried because of the long illness and pain and lack of income during this period. A short while before he died an electrocardiogram was taken which was interpreted by his physician

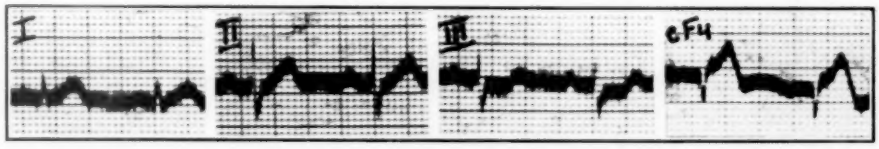

Fig. 1.—Case 2. 6-19-1947. Tracings interpreted by physicians as indicative of acute anterior coronary thrombosis. Note early take-off of S-T_1 and slightly depressed S-T_3 and definitely elevated S-T in lead CF_4 with an absence of R wave in this lead.

Fig. 2.—Case 2. Arrow point to occluding emboli in several medium-sized pulmonary arteries in the left lung.

as confirming the diagnosis of acute coronary thrombosis with anterior myocardial infarction (Fig. 1). The physicians in attendance did not think an autopsy was necessary, as they felt that the diagnosis was certain and therefore a postmortem examination was not performed.

The following was part of the reply sent to the attorney 3 months after death of the patient:

". . . I am not at all certain that this man died of an acute coronary thrombosis, despite the electrocardiographic report. I have seen frequent instances where the electrocardiograms were misinterpreted. There is particular confusion between electrocardiograms of an acute coronary thrombosis and those from a pulmonary embolism. Very often after an injury when the patient is supposed to have died of an acute coronary thrombosis, the sequence is as follows: after a blow to a limb, a thrombophlebitis develops (inflammation of the vein). This can occur 1 or 2 weeks after the injury. Within a few days or a few weeks later a clot becomes dislodged from the phlebitis, lands in the lungs, and is fatal. The symptoms produced by this terminal event are not unlike those produced by a coronary attack. Even the electrocardiograms of one may resemble those of the other. I had a medicolegal case not unlike yours, in which I advised the body be disinterred a couple of months after burial, for postmortem examination. This was done and proved that my suspicion was correct. The man had nothing abnormal in his heart and had a pulmonary embolism from a phlebitis of the leg. It changed the entire legal aspect of the case, for under such circumstances there is no question whatever that the accident is the direct and sequential and only cause of death."

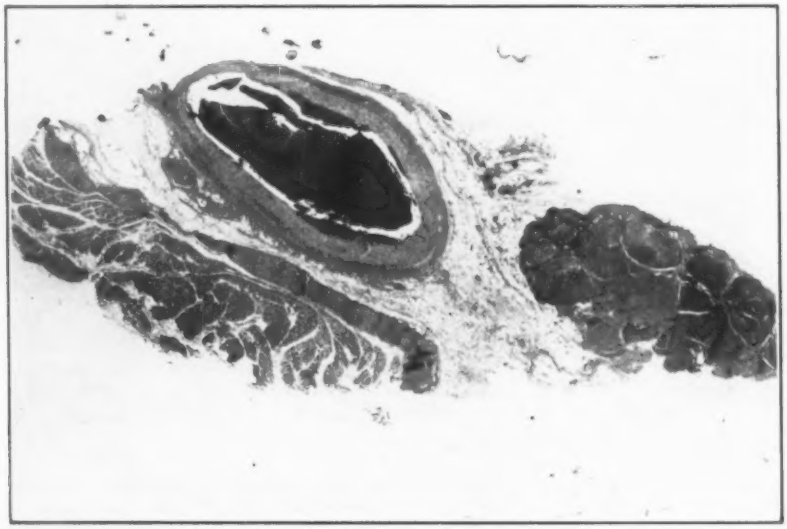

FIG. 3.—Case 2. A recent thrombus is seen in a small calf vein of the left leg. Note its partial attachment to the intima.

As a result of the advice given the body was exhumed on November 14th, 1947, and an autopsy was performed. A large pulmonary embolus was found plugging the main left and right pulmonary arteries; numerous emboli were present in the branches of the left lung (Fig. 2) and there were 3 hemorrhagic infarcts of the left lower lobe. Similar findings were present in the right lower lobe as well. Examination of the veins of the right leg showed no large thrombi but showed some smaller ones in the veins of this lower extremity. On microscopic examination a recent thrombus was found in a vein of the left calf with subintimal proliferation and cellular infiltration of the intima (Fig. 3). The heart weighed 300 gm., there were only minimal arteriosclerotic changes in the coronary vessels, but no evidence of thrombosis either recent or old. The valves, endocardium, myo-

cardium, and pericardium were normal throughout.

After the postmortem examination, the insurance company made a reasonable settlement and the widow obtained her deserved compensation.

Comment. The above described cases illustrate a few simple but inadequately appreciated clinical observations. In the first place, the differential diagnosis between acute coronary thrombosis and acute pulmonary embolism is quite difficult. Absolute reliance on the electrocardiogram when the changes are not classical and when repeated tracings cannot be obtained may be misleading. Although in these two instances, the physicians interpreted the electrocardiograms as indicative of anterior myocardial infarction, more commonly an acute pulmonary embolism may simulate posterior myocardial infarction. In the second place, when some cardiorespiratory emergency develops after trauma, it is much more frequently the result of pulmonary embolism than a coronary attack. One should therefore search diligently for evidence of thrombophlebitis in the legs and regard a pulmonary embolism as the more likely one of the two conditions, even if no site for the origin of the embolus can be detected. Finally, if an autopsy has not been performed, as was the case in these two instances, disinterring the body and examination of the heart and lungs even months after death may serve as a valuable and decisive means to determine the cause of death and to solve equitably a controversial medico-legal problem. This is important because, whereas there may be doubt as to the role of an accident as a cause of a subsequent fatal coronary thrombosis, there can be no doubt about an accident causing a local thrombophlebitis, pulmonary embolism, and death. There is very little in our medical literature that deals with disinterring the body to solve medico-legal controversies such as have been described here. Hamman[1] and White[3] had similar experiences, each with a single case.

Summary. Two cases, almost identical, are reported in which death was presumed to have occurred from coronary thrombosis, weeks or months after traumatic injury of the leg. In both cases litigation developed as to whether the death was due to the accident. We suggested that the clinical diagnosis might well have been incorrect and that the bodies be disinterred to seek for phlebitis and pulmonary embolism as the probable causes of death. Such was found to be the case in each instance and the widows, who probably otherwise would have lost their suits, readily obtained their just compensation.

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MAJOR SURGERY IN PATIENTS WITH HEALED MYOCARDIAL INFARCTION

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Surgery is frequently withheld from patients who have had previous coronary occlusions because they have been considered poor operative risks. Our experience at Memorial Center for Cancer and Allied Diseases with 58 patients subjected to major surgery despite healed myocardial infarctions suggests that such patients should not be denied surgical care of cancer.

Butler, Feeney, and Levine[2] have said that although coronary artery disease materially increases the operative risk, operations can be carried out with reasonable security if delayed until a satisfactory recovery from the coronary thrombosis has occurred. In 8 patients with healed myocardial infarction there was 1 postoperative death. In 35 patients with angina subjected to surgery there were 3 deaths.

Brumm and Willius[1], in a review of 257 patients with the anginal syndrome subjected to surgery at the Mayo Clinic, found that 11 of these patients died as a result of cardiac complications postoperatively. Of the 257 patients, 32 were said to have healed myocardial infarction. Morrison[4], in a review of 478 patients with heart disease subjected to 701 operations at New York Hospital between 1933 and 1943, included 25 patients with previous coronary occlusions and 41 patients with angina. There were 3 postoperative deaths in the former group and 5 in the latter. Since 1943 there have been improvements in preoperative, operative, and postoperative care with respect to electrolyte management, anesthesia techniques, blood replacement, intestinal decompression, and antibiotics with wider ranges of activity. As a result, the patient has a better chance to survive the operation and any postoperative complications.

Because untreated cancer is invariably fatal, surgery may be employed more liberally than in other diseases where surgery is elective. Since cancer occurs in the age groups in which degenerative cardiovascular diseases are prevalent, we have had an excellent opportunity at Memorial Center to observe the response to surgery of the patient with degenerative heart disease.

In this communication the authors have attempted to answer the following questions: 1) Do patients with healed myocardial infarctions undergoing surgery have an unusually high immediate mortality? 2) Do patients with healed myocardial infarctions have an unusually high incidence of postoperative cardiorespiratory complications? 3) Does the surgical procedure cause an acceleration or

aggravation of the cardiac disease as manifested clinically or by electrocardiographic tracings? 4) Is the incidence of cardiorespiratory complications influenced by such factors as anesthesia, type and length of operation, cardiac classification, past cardiovascular history, heart size, administration of blood or other parenteral fluids?

Method of Study. Fifty-eight electrocardiographic tracings, taken between 1946 and 1950, and compatible with a diagnosis of healed myocardial infarction were collected. No tracings with bundle branch block were included. Our criteria for healed infarctions were[3,6]:

1. Posterior wall infarction:
   a) Q in lead 3 equal to or greater than 75% of the tallest R wave in any limb lead.
   b) Wide Q wave in lead 3 (more than 0.04 sec.).
   c) Deep inversion of T wave in lead 3 (more than 2.5 mm.).
   d) No displacement of ST segment.

In addition, one or more of the following were present.

   e) Absence of S wave in lead 1.
   f) Q wave in lead 2, 1 mm. or more.
   g) Low T wave in lead 2 (less than 1 mm.).

2. Anterior wall infarction:

The presence in the precordial leads V3, 4, 5, and 6 of 1 or more Q waves of the following patterns:

   a) The depth of Q is 25% or more of the amplitude of the R wave, or the entire QRS complex may consist of a QS deflection.
   b) The width of Q is 0.04 second or more.

The 58 patients with electrocardiographic evidence of healed infarction were subjected to the operations listed in Table 1. Information was assembled from the charts for each patient with reference to: age, sex, past cardiovascular history, the New York Heart Association classification of the heart diseases, cardiac size, blood pressure, preoperative management, the anesthesia, the operative and postoperative course, the effect of parenteral fluids given postoperatively, and the complications encountered, with special attention to those of the cardiorespiratory system.

Results of Preoperative Evaluation. Of the 58 patients, 24 gave histories of previous coronary occlusions; and, of these 24 patients, the most recent episode was 6 months, and the most remote, 15 years. Eight of the 24 gave a history of angina, while 5 of the remaining 34 had a history of angina. Two of the 34 patients without history of previous coronary occlusion had had congestive heart failure. There were 45 males and 13 females. There was sustained hypertension (diastolic over 90, systolic over 140, or both) in 32 patients. The average age was 61.9 years with the youngest patient being 41 and the oldest 78. There was Roentgen-ray evidence of cardiac enlargement in 11 patients. No roentgenograms of the chest were taken in 10 patients. According to the criteria of the New York Heart Association, there were 6 patients in Class 1A, 20 in 1B, 11 in 2B, 13 in 2C, 7 in 3C, and 1 in 3D. Preoperatively, 3 patients were given quinidine and 16 were digitalized; in 2 others maintenance doses of digitalis were continued.

Operative and Postoperative Course. In Table 1 the operations and the anesthetic agents are listed. In none of these operations was it necessary to terminate the procedure because of concomitant complications. In 7 patients there was a drop in diastolic pressure of more than 20 mm. of mercury for 10 minutes, but a return to normal levels was obtained by the use of neosynephrine subcutaneously or by whole blood transfusions except in 1 instance. In this 1 patient (Case 3) the diastolic pressure remained 25 mm. below the preoperative level for the last half hour of the operation and continued to fall postoperatively, with the patient dying in shock. Ether anesthesia was used in 26 patients, spinal in 12, and pentothal in 14; local anesthesia was used in 6 instances. Oxygen was

TABLE 1.—OPERATIONS PERFORMED AND TYPE OF ANESTHESIA USED IN 58 CASES SHOWING ELECTROCARDIOGRAPHIC EVIDENCE OF HEALED INFARCTION

Type of Operation	*No.*	*Ether*	*Spinal Anesthesia*	*Pentothal Anesthesia*	*Novocaine Anesthesia*
Subtotal gastrectomy with resection of pancreas and spleen	1	1			
Resection of duodenum and head of pancreas	1	1			
Abdomino-perineal resection	8	3	5		
Total gastrectomy	2	2			
Subtotal gastrectomy	5	3	2		
Abdomino-perineal cystectomy and prostatectomy	2	2			
Radical neck dissection	7			7	
Radical hysterectomy with node dissection	1	1			
Excision of cervical stump with node dissection	1	1			
Hysterectomy	1	1			
Resection mandible and floor of mouth	1			1	
Total laryngectomy	2			1	1
Mastectomy and axillary dissection	3	3			
Bilateral uretero-enterostomy	1	1			
Thyroidectomy	2			1	1
Sigmoid resection	1	1			
Appendectomy	1		1		
Vulvectomy	1	1			
Partial laryngectomy	1				1
Excision of groin tumor and orchidectomy	1	1			
Laparotomy	3	2	1		
Colostomy	2	1	1		
Suprapubic cystotomy	3	1	1		1
Excision of bilateral parotid tumors	1			1	
Excision of breast duct system	1			1	
Tracheostomy	2				2
Excision buccal and lip leukoplakia	1			1	
Transurethral resection of bladder papilloma	1		1		
Excision of carcinoma of ear	1			1	
	58	26	12	14	6

TABLE 2.—POSTOPERATIVE COMPLICATIONS DIVIDED INTO CARDIORESPIRATORY AND NON-CARDIORESPIRATORY IN 26 PATIENTS

Cardiorespiratory Complications (14 patients)	
Myocardial Infarction	4
Angina	1
Congestive Failure	5
Pulmonary Infarct	1
Bronchopneumonia	4
Atelectasis	1
Prolonged Post-operative Hypotension	1

Non-Cardiorespiratory Complications (16 patients)	
Shock with death post-operatively	1
Pneumothorax	1
Meningitis	1
Alkalosis	1
Mild diabetic acidosis	1
Uretero-vaginal fistula	1
Pharyngeal fistula	1
Transient psychosis	1
Abdominal distention	3
Wound abscess	1
Wound bleeding	1
Unexplained fever	2
Bilateral parotitis	1
Penicillin reaction	2

administered during the operation to 36 patients. The length of operations was less than 1 hour in 8 patients, 1 hour to 1 hour and 59 minutes in 15, 2 hours to 2 hours and 59 minutes in 19 patients, and greater than 3 hours in 16. Twenty-one patients received no blood during the operative and immediate postoperative periods; 13 received 500 to 999 cc., and 24 received more than 1000 cc. Postoperatively, 32 patients received 0 to 1499 cc. of intravenous fluids, 10 received a maximum of 1500 to 3000 cc. for a 24-hour period, and 16 received more than 3000 cc. for a 24-hour period.

In the postoperative periods, 3 patients died within the first 30 days, an operative mortality of 5.2%. A high percentage of patients (24.1%) developed some form of cardiorespiratory complication and 2 of these patients died. In Table 2 are recorded the postoperative cardiorespiratory and non-cardiorespiratory complications. Four patients developed acute myocardial infarctions after operation. One of these patients (Case 2) developed substernal tightness on the 2nd postoperative day with electrocardiographic evidence of acute anterior infarction. He died suddenly, presumably of coronary occlusion, on the 11th postoperative day. None of the other 3 patients had symptoms of coronary occlusion, the diagnosis of infarct being made on the basis of electrocardiographic changes. One patient's electrocardiogram, which had had deep Q's in leads 2 and 3 with sharply negative T's in 2 and 3 and high T's in the CF leads, showed on the 11th postoperative day Q's in CF3 and CF4 with decrease in amplitude of the precordial T waves and development of upright T's in lead 3. These changes were thought to be consistent with extension of a posterior infarct to the apex. Recovery was uneventful. The 3rd patient's electrocardiogram, which had shown Q's in leads 2 and 3 with sharply inverted T's in leads 2 and 3, showed on the 4th postoperative day elevation of the ST segment in leads 2 and 3 consistent with extension of his old posterior infarct. Subsequently, following the intravenous administration of large amounts of saline solution and plasma to combat postoperative alkalosis, he developed congestive heart failure and was treated with mercurial diuretics, digitalis, and fluid restriction, with uneventful recovery. The other patient's electrocardiogram, which had shown Q waves in leads 2 and 3 with inverted T3 and low T2, showed, on the first postoperative day, elevation of the ST segment in leads 2 and 3 with depression of ST1 and inversion of T1. These changes were consistent with recent extension of his old posterior infarct; recovery was uneventful. The 1 patient who developed angina postoperatively did so on the 5th day, and her electrocardiogram showed no acute change.

Five patients developed mild postoperative congestive heart failure which readily responded to digitalization, diuretics, and fluid restriction. Four patients developed bronchopneumonia which cleared rapidly in 3 patients; the 4th (Case 1) had a complicating tracheitis with atelectasis and died. One patient whose preoperative blood pressure was 200/120 maintained a postoperative pressure of 108/80 for 8 to 10 hours; this rose to preoperative levels following transfusion of blood. A pulmonary embolus occurred in a patient 2 weeks following hysterectomy.

There was 1 autopsy among the 3 patients who died. This death (Case 1) was due to preoperative tracheitis which was the main complicating factor leading to postoperative atelectasis and bronchopneumonia. One death (Case 2) was apparently due to coronary

occlusion. The 3rd death occurred 50 minutes postoperatively while the patient was in shock of unknown etiology.

Case Reports on Deaths. CASE 1. C. B., a 56-year old white male, who 6 months previously had undergone a total laryngectomy for carcinoma of the intrinsic larynx, entered the hospital on December 6, 1946, with neck node metastases. His previous health, except as related to his present illness, was good. He did have some difficulty in cleaning his tracheostomy opening due to mucous plugs. Physical examination revealed a well developed and well nourished white man with a blood pressure of 140/88. The heart was not enlarged, and the rhythm was normal sinus with a rate of 88. The lungs were clear and there was no ankle edema. In the neck was a tracheostomy opening that appeared clear. There was an 8 x 5 cm. left digastric mass. The electrocardiogram showed a low T2 and sharply inverted T3 with Q's in leads 2 and 3; these findings were thought to be consistent with old posterior infarct. The heart on Roentgen-ray examination was not found to be enlarged. On December 9, 1946, a left neck dissection with removal of the anterior portion of the pharynx was done under sodium pentothal anesthesia. The procedure lasted 4 hours; 500 cc. of blood were given and there was no significant depression of blood pressure. Postoperatively there was difficulty in keeping the tracheostomy opening cleared because of dried mucous plugs which had to be removed by frequent suctioning and, on occasion, by bronchoscopy. A pharyngeal fistula developed. On the 12th postoperative day, his temperature was 103° F., and clinically this was thought to be due to atelectasis and areas of pneumonitis. On the 14th postoperative day the patient suddenly expired.

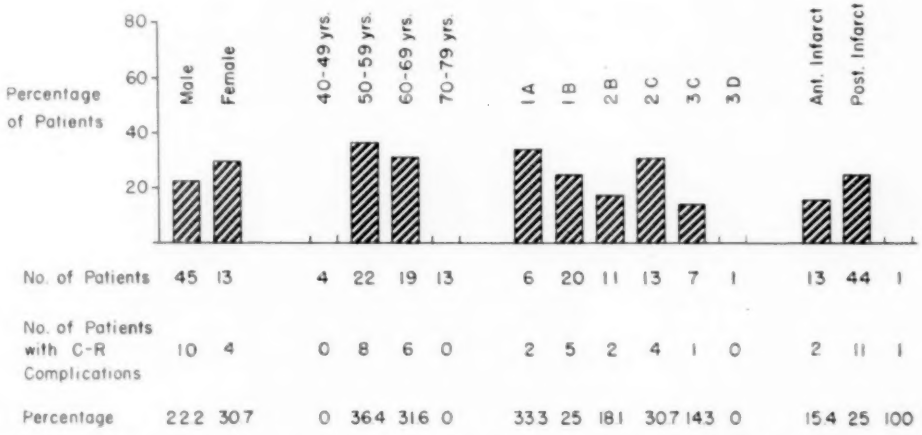
At postmortem examination the heart weighed 375 gm. The coronary arteries were tortuous and sclerotic with the circumflex branch completely occluded. There was a 5 x 3 cm. area of fibrosis in the posterior wall of the left ventricle extending to the septum. There was an acute tracheitis with ulcerations of the carina. In the lungs there were broncho-pneumonia and areas of partial atelectasis bilaterally.

CASE 2. A. S., a 65-year old white male, entered the hospital on March 4, 1948, complaining of rectal bleeding of 2 weeks' duration. He had had a coronary occlusion 15 years previously, and since then had had frequent anginal attacks. There was no dyspnea, edema, or palpitation. Physical examination revealed a well developed and well nourished man with a blood pressure of 144/86. His heart was not enlarged, and there was a normal sinus rhythm. Lungs were clear, and there was no peripheral edema. There was a friable mass on the posterior wall of the rectum. The heart was not enlarged on Roentgen-ray examination. The electrocardiogram on March 6, 1948, showed low R's in CF3 and 4 but no Q's in the precordial leads. On March 10, 1948, a combined abdomino-perineal resection of the rectum under spinal anesthesia was done. The patient withstood the procedure well and returned to the floor in good condition. On the 2nd postoperative day he developed tightness in his chest relieved by opiates and oxygen. His heart rate was regular and rapid. There were occasional crackling rales at both bases. The electrocardiogram showed the appearance of Q waves in CF3 and CF4 with slight elevation of the ST segments. There was a Q in lead 3. The chest film showed bronchopneumonia at the right base. A repeat electrocardiogram the following day showed Q waves in CF3, 4, and 5 with slight elevation of the ST segment in 3. He did fairly well subsequently except for frequent episodes of squeezing substernal pain. He expired suddenly on the 18th hospital day and no autopsy was obtained.

CASE 3. A. C., a 58-year old white male, entered the hospital on April 16, 1947, with a history of hematuria of 1 month's duration. He had had diabetes mellitus for 20 years and this was controlled with insulin and diet. The physical examination revealed that his heart was not enlarged, and his blood pressure was 140/80. The lungs were clear, and there was no evidence of peripheral edema. The electrocardiogram showed Q's in leads 2 and 3 with a sharply inverted T3. The heart was not enlarged on Roentgen-ray examination. On April 26, 1947, the left ureter was transplanted to the skin in a 1½ hour procedure done under spinal anesthesia. There was no significant blood pressure drop and 500 cc. of blood were given. Postoperatively he did poorly and was digitalized for tachycardia. He developed bronchopneumonia and atelectasis at the left base. Postoperative electrocardiograms showed T wave changes thought to be due to digitalis. On May 10, 1947, under ether anesthesia an abdomino-perineal cystectomy was done. The blood pressure was well maintained during the 3-hour procedure except for the last half-hour, when it dropped to 90/60. Fifteen hundred cc. of blood were given during the procedure. On return to the floor, the blood pressure was 80/40, and he was in peripheral

shock without evidence of cardiac failure. He died 50 minutes postoperatively, and no autopsy was obtained.

Analysis of Cardiorespiratory Complications. *Sex, Age, Cardiac Classification, Location of Infarct.* The correlations of cardiorespiratory complications with sex, age, cardiac classification, and locus of infarct are shown in Graph 1. Of the 45 males there were 10 (22.2%) with cardiorespiratory complications. Among the 13 women, there were 4 with cardiorespiratory complications (30.7%). These differences were felt to be insignificant. None of the 4 patients between 41 and 49 years of age had cardiorespiratory complications; of 22 patients between 50 and 59, 8 had such complications (36.4%). There were 19 patients between the ages of 60 and 69, 6 with cardiorespiratory complications (31.6%). It is interesting that among 13 patients 70 to 78 years of age, there were none with cardiorespiratory complications although surgery was no less extensive in this age group (there were 10 abdominal operations, 2 on the head and neck, and 1 mastectomy). Six of these patients received more than 1000 cc. of blood at operation and immediately thereafter. Only 3 of this group gave a history of infarct; 2 had had angina. A possible explanation of the low cardiorespiratory complication rate in this age group might be the efficiency of their collateral circulation, but the number of patients is too small to permit conclusions.



Graph 1.—Correlations of sex, age, cardiac classification (N.Y. Heart Association, functional and therapeutic), and location of infarct with cardiorespiratory complications. In this graph and the 3 following, the percentages of patients with cardiorespiratory (C-R) complications among patients of various groups are shown.

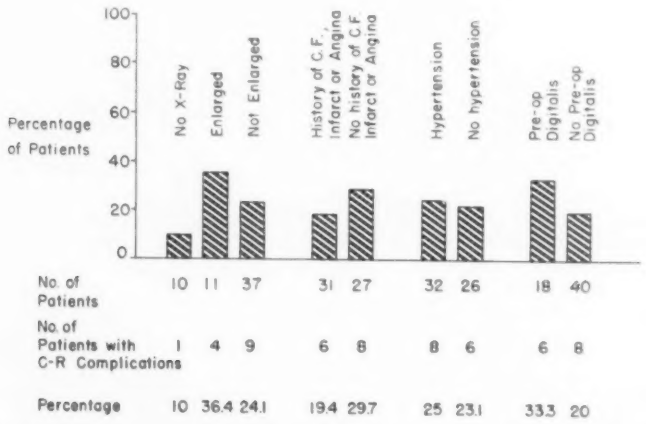
Six patients were in Class 1A and 2 (33.3%) had complications. In Class 1B there were 20 patients; 5 (25%) had cardiorespiratory complications. Of 11 patients in Class 2B, 2 (18.1%) had complications; of 13 in Class 2C, 4 (30.7%) had complications. In Class 3C, complications occurred in 1 (14.3%) of 7 patients. The 1 patient in Class 3D had no complications. Because of the small number of patients studied, no conclusions can be made with regard to the value of the clinical estimation of cardiac function and the incidence of postoperative complications. However, we

would certainly have expected more complications among Class 4 patients.

There were 13 patients with anterior infarcts, and 2 of these (15.4%) had cardiorespiratory complications. Twenty-five %, or 11 out of 44, of the patients with posterior infarcts developed complications. One patient who had both an anterior and a posterior infarct developed congestive heart failure. These differences are not significant, but a 24% over-all incidence of cardiorespiratory complications is high.

complications. On the other hand, of the 27 with no history of past cardiovascular difficulty, there were 8 (29.7%) with cardiorespiratory complications. This difference may be significant but perhaps may be a reflection of the greater care given to patients having a history of previous cardiovascular difficulty.

Among the 32 patients with hypertension, 8 (25%) developed cardiorespiratory complications; in 26 patients without hypertension there were 6



GRAPH 2.—Correlations of heart size, past cardiovascular history, hypertension, use of preoperative digitalis with cardiorespiratory (C-R) complications. (cf.: Congestive Heart Failure).

Heart Size, History, Hypertension, Digitalization. The correlations of cardiorespiratory complications with heart size, past cardiovascular history, hypertension, and preoperative digitalization are shown in Graph 2.

Of the 11 patients with Roentgen-ray evidence of cardiac enlargement, 4 (36.4%) developed such complications. Of 37 patients with Roentgen-ray evidence of normal heart size, 9 (24.1%) had complications. These differences are slight.

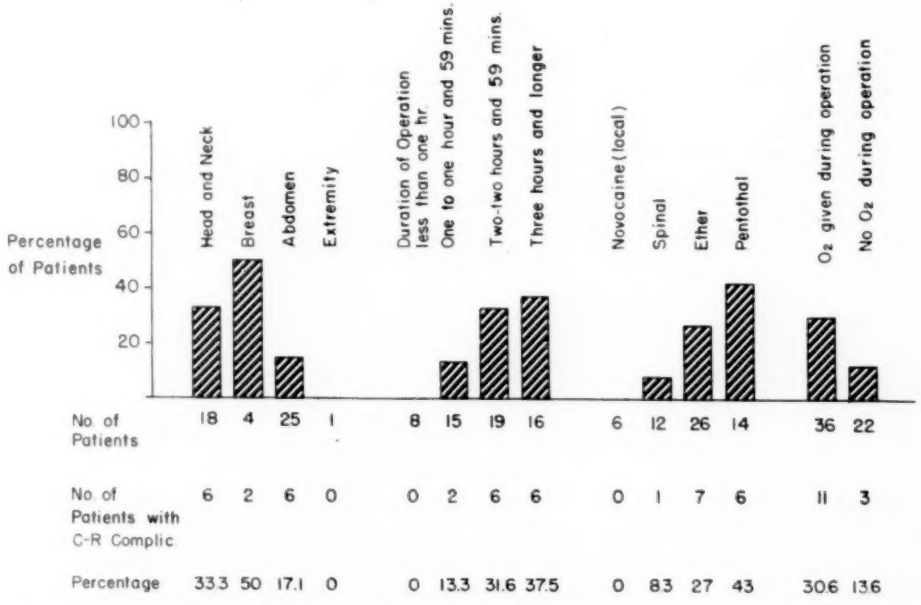
Thirty-one patients gave a history of angina, previous coronary occlusion, or congestive heart failure; 6 of these (19.4%) developed cardiorespiratory

(23.1%) with complications. These figures suggest that hypertension per se played no role in the increased incidence of cardiorespiratory complications.

Cardiorespiratory complications appeared in 6 (33.3%) of 18 patients digitalized preoperatively and in 8 (20%) of the 40 not given digitalis. The slightly increased incidence of complications in the digitalized patients is probably related to the severity of their heart disease, since half (50%) of the complications encountered in this group consisted of postoperative congestive heart failure. This developed in only 2 patients not given digitalis.

Operation, Anesthesia, Oxygen. The correlations of cardiorespiratory complications with type and length of operation, anesthetic agent, and use of oxygen during the operation are shown in Graph 3. Of 18 patients who underwent operations in the head and neck regions, there were 6 (33%) with cardiorespiratory complications; 3 developed congestive heart failure, 1 postoperative hypotension, 1 angina, and 1 pneumonia with atelectasis and tracheitis. Of 4 patients subjected to breast operations, 2 developed cardiorespiratory complications. Abdominal procedures were performed in 35 patients, 6 of whom (17.1%) developed cardiorespiratory complications. The 1 patient subjected to a procedure on his extremity had no complications. There seems to be an excessively high incidence of cardiorespiratory complications in the patients undergoing head and neck surgery; however, all 4 of the patients who developed acute myocardial infarcts were in the group having abdominal surgery. No correlation between the incidence of complications and the use of a Levine or nasal tube was evident.

It may be seen from Graph 3 that as the length of the operative procedure increases, so does the rate of the cardiorespiratory complications. The 8 patients whose operations were completed in less than 1 hour had none of these complications. Of 15 patients whose operations lasted beween 1 hour and 1 hour and 59 minutes, there were 2 (13.3%) with such complications. There were 6 patients (31.6%) with cardiorespiratory complications among the 19 whose operations lasted between 2 hours and 2 hours and 59 min-


Percentage of Patients
100
80
60
40
20
Head and Neck
Breast
Abdomen
Extremity
Duration of Operation
less than one hr.
One to one hour and 59 mins.
Two-two hours and 59 mins.
Three hours and longer
Novocaine (local)
Spinal
Ether
Pentothal
O2 given during operation
No O2 during operation
No. of Patients 18 4 25 1 8 15 19 16 6 12 26 14 36 22
No. of Patients with C-R Complic. 6 2 6 0 0 2 6 6 0 1 7 6 11 3
Percentage 33.3 50 17.1 0 0 13.3 31.6 37.5 0 8.3 27 43 30.6 13.6

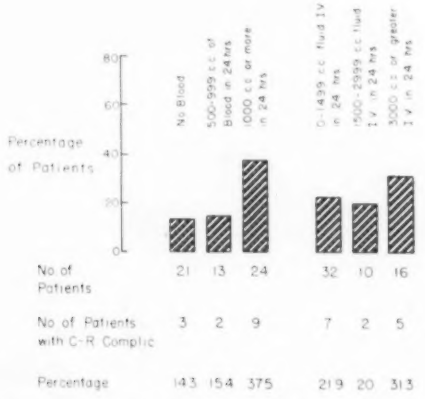
GRAPH 3.—Correlations of type of operation, duration of operation, type of anesthesia, use of oxygen during operation with cardiorespiratory (C-R) complications.

utes. Of the 16 patients whose operations took 3 hours or more, 6 (37.5%) developed complications.

Among 6 patients in whom local anesthesia was used there were no complications. Of 12 patients having spinal anesthesia, only 1 (8.3%) developed a cardiorespiratory complication. Of 26 patients in whom ether was used, there were 16 (27%) with complications. Of 14 patients receiving pentothal there were 6 (43%) with complications. Pentothal was used, with one exception, only in the head and neck group. We have already seen that a complication rate of 33.3% occurred in the head and neck group; 5 similar patients had comparable operations done under local anesthesia without complications. This means that, of the 13 patients having had head and neck operations with pentothal, 6 developed complications. Consequently, it would seem that the high incidence of complications in the head and neck group may well have been related to the anesthetic, pentothal, and not to the region of the surgery.

Oxygen was administered at the operating table to 36 patients and 11 (30.6%) of these developed cardiorespiratory complications. Of the 22 who were not given oxygen, only 3 developed these complications (13.6%). Just as with the prophylactic use of digitalis, the administration of oxygen was thought necessary in those patients having the poorest cardiac reserve.

Transfusions and Fluids. Correlations between cardiorespiratory complications in relation to maximum volume of blood administered in 24 hours and maximum volume of other intravenous fluids in 24 hours are shown in Graph 4. Three of 21 patients (14.3%) not given blood developed complications. Two had congestive heart failure and 1 a pulmonary infarct. Two of 13 patients (15.4%) given 500 to 999 cc. of blood developed complications. Twenty-four patients received more than 1000 cc. of blood with 9 (37.5%) developing complications. This correlation may be fallacious, since blood was usually given when the operative procedure lasted 2 or more hours; in these cases correlations were high between the following: complication rate and the amount of blood given; complication rate and the duration of operation;


Percentage of Patients
80
60
40
20
0
No Blood
500-999 cc. of Blood in 24 hrs.
1000 cc. or more in 24 hrs.
0-1499 cc. fluid IV in 24 hrs.
1500-2999 cc. fluid I.V. in 24 hrs.
3000 cc. or greater I.V. in 24 hrs.
No. of Patients 21 13 24 32 10 16
No. of Patients with C-R Complic 3 2 9 7 2 5
Percentage 14.3 15.4 37.5 21.9 20. 31.3

GRAPH 4.—Correlations of maximum volume of blood given in 24 hours and maximum volume of other intravenous fluids in 24 hours with cardiorespiratory complications.

the duration of operation and the amount of blood administered.

There seemed to be no relation between the maximum amount of fluid given for any 24-hour period and the complication rate. Of 32 patients who received 0 to 1499 cc. of intravenous fluids, 7 developed complications, including 3 instances of congestive heart failure. Two of 10 patients who had 1500 to 3000 cc. of intravenous fluids developed complications. Five of 16 (31.3%) who received more than 3000 cc. of fluid developed complications, as compared to 21.9% and 20% for the first 2 groups mentioned. The intravenous fluid was given slowly in all instances, and the patients were watched for appearance of congestive heart failure. It would seem that patients with myocardial infarction may tolerate a surprisingly large amount of fluid cautiously given.

TABLE 3.—END RESULTS AT DIFFERENT POSTOPERATIVE PERIODS IN 58 PATIENTS WITH ELECTROCARDIOGRAPHIC EVIDENCE OF MYOCARDIAL INFARCTION

	0–19 days	*3 weeks–3 months*	*¼–6 months*	*7–11 months*	*12–23 months*	*Greater than 2¼ months*
Immediate Postoperative Deaths	3					
Deaths from Carcinoma		2		4	4	1
Deaths—Cause not Determined		3	1	3	1	
Deaths—from Heart Disease				1	1	
Surviving Patients with Increasing Cardiac Symptoms					1	1
Surviving Patients without Increasing Cardiac Symptoms	1	2	1	2	4	3
Surviving Patients without Cardiac Symptoms	1	2	1	1	5	9

Results: Follow-up Studies. In Table 3, the follow-up studies on the 58 patients are presented. There was an immediate postoperative mortality of 5.2%. Eleven patients have since died of cancer. Eight have died of unknown causes. Two patients have died of heart disease, one at home 9 months postoperatively of a coronary occlusion, and one 2 years later while in the attending surgeon's office, presumably of coronary occlusion. Two patients in the group with increasing cardiac symptoms developed coronary occlusions 1½ and 24 months postoperatively. One of these patients subsequently developed angina, and the other had an uneventful recovery without subsequent cardiac distress. Two patients were lost to follow-up. Twelve patients have survived 3 weeks to greater than 24 months without increasing cardiac symptoms. Eighteen patients lived 3 weeks to more than 2 years without cardiac symptoms.

Discussion. The 5.2% mortality of our 58 patients with evidence of healed myocardial infarction compares favorably with the 3.4% mortality among 260 patients 60 to 71 years of age subjected to similar, major surgical procedures[5]. An incidence of 24.1% of cardiorespiratory complications, however, seems excessive and was probably in large part related to the presence of degenerative cardiovascular disease. The presence of pulmonary vascular congestion in an elderly bed-ridden patient is almost always associated with bronchopneumonia, the latter leading to further anoxemia, aggravation of congestive heart failure, the development of cardiac arrhythmias, and possibly embolism. The cardiorespiratory complications seen were as follows: 4 patients developed fresh myocardial infarcts; 4 patients had bronchopneumonia; 1 pa-

tient developed a pulmonary embolism; 5 patients had congestive heart failure. Some of these patients had multiple complications. The 3 deaths were ascribed to operative shock, myocardial infarction, and tracheitis.

None of the patients developed arrhythmia, and in none was it necessary to terminate the operation because of shock or other cardiorespiratory complications. Because of limited electrocardiographic data it was not possible to estimate the size of the infarct. The problem of emergency surgery in the presence of acute infarction was not studied. Urgent or elective surgery should be delayed for at least 6 weeks following acute myocardial infarction. The closest cooperation among surgeon, anesthetist, and internist is essential to the care of these patients. They must be closely watched so that treatment can be altered to suit the immediate needs in any changing situation.

The need for digitalis was associated with an increased complication rate, as might have been expected, since the drug was given to those patients having the greatest evidence of cardiac disease.

Operations done in the head and neck region were accompanied by a high complication rate, but we feel that the type of anesthesia (pentothal) given these patients was a more likely offender than the type of surgery. The cardiorespiratory complication rate was 43% for patients given pentothal, 27% for those given ether, 8.3% for spinal anesthesia, and zero for operations done under local anesthesia. As the length of operation increased, so did the complication rate; no complications were noted when the surgery lasted less than 1 hour; 13% developed after operations of 2 hours or less, and complications appeared in 31.6% of patients undergoing operations of 2 to 3 hours' duration, and 37.5% in those of longer than 3 hours. Surprisingly, the complication rate was the same for patients given no blood or parenteral fluids as for those receiving up to 1000 cc. of blood and 3000 cc. of parenteral fluid, or both. When greater amounts of blood or fluids were given, the complication rate was nearly double and almost identical with the rate seen when the operation lasted more than 2 hours. Indeed, all patients given large amounts of blood or parenteral fluids had operations lasting 2 or more hours.

The operation per se did not appear to aggravate the heart disease, since only 2 of the survivors developed increasing cardiac symptoms. Two patients died of heart disease 9 and 18 months respectively, after leaving the hospital. Fourteen patients were alive 2 or more years after their surgery, and 16, 1 or more years. These patients would have succumbed to cancer had they been denied surgical care because they were poor operative risks.

Conclusions. 1. Evidence of healed myocardial infarction is not a contraindication per se to adequate surgical care of cancer. Fifty-eight such patients were operated upon with a mortality rate of 5.2%.

2. Twenty-four per cent of these patients developed postoperative cardiorespiratory complications.

3. The incidence of cardiorespiratory complications was apparently greater in patients who had cardiac enlargement but was seemingly unrelated to sex, age, cardiac classification (1A to 3C), age of infarct, angina, or hypertension.

4. The longer the surgical procedure, the greater the complication rate became.

5. Pentothal anesthesia was associated with a 43% incidence of cardiorespiratory complications.

6. Such patients tolerate moderate

amounts of whole blood and intravenous fluids surprisingly well.

7. The adequate surgical care of cancer in a patient who has a healed myocardial infarct does not appear to affect adversely the existing heart disease.

8. Fourteen of these patients were alive 2 or more years after their operations and 16 survived 1 or more years.

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IRREVERSIBLE POST-HYPOGLYCEMIC COMA*

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The clinical and metabolic disturbances occurring as the result of hypoglycemia may, in most instances, be completely reversed by the administration of glucose. We have had the opportunity of studying cerebral hemodynamics and oxygen utilization in 4 patients with persistent post-hypoglycemic coma in whom administration of glucose had no apparent influence on the condition, which terminated fatally. Although numerous cases of this type have been reported previously[1,3,13,14,18,19,23,24,26,29], quantitative studies of the circulatory and metabolic characteristics of the central nervous system in this condition so far have been lacking.

Material and Methods. The 4 patients studied were known diabetics each of whom had been admitted to the hospital on one or more other occasions because of acidosis or insulin reactions. On final admission 2 were deeply comatose due to moderately severe or severe hypoglycemia of unknown duration and previous degree; in the other 2 subjects hypoglycemia had been inadvertently induced during the course of vigorous treatment for diabetic acidosis. All patients, following demonstration of hypoglycemia, failed to show a clinical response to intravenous dextrose. In every case a thorough search for causes of continuing coma was without positive result. The patients remained in coma until death, for periods varying from 3 days to 3 weeks, during which time the blood sugar was maintained well above normal levels. Studies of cerebral hemodynamics and oxygen consumption were performed at intervals, using the nitrous oxide method of Kety and Schmidt[15] as modified by Scheinberg and Stead[25]. Electroencephalograms were recorded with a Grass 6-channel instrument.

Results. The accompanying table presents the values obtained in the subjects of this investigation. The basis for comparison is the result of similar studies in 17 unselected hospital patients, ranging in age from 23 to 57 years, without specific central nervous system disturbances. The range of values in this group represents a combination of biological variation and error of the experimental method.

In only 1 of the subjects with post-hypoglycemic coma did the cerebral blood flow consistently show a marked alteration from the normal. A tendency toward progressive reduction in flow appears to have been demonstrated by repeated studies in Patients 1 and 2. The "vasomotor center" responsible for maintaining general peripheral vascular tonus in all subjects must have remained relatively intact, since in no patient was there observed an abnor-

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mal depression of arterial blood pressure and in cases 1, 2, and 4 it showed no significant change in the course of several observations. Cerebral vascular resistance in Cases 1 and 2 consequently showed a progressive increase related mathematically to the progressively reduced cerebral blood flow.

In Patient 1, who survived for 3 weeks, the cerebral metabolic rate initially approached the lower limit of the normal range. In patients 2 and 4, who lived for 2 weeks and 1 week, respectively, after their hypoglycemic episodes, there was initially a moderate to marked reduction in cerebral oxygen consumption, and in Patient 3, who survived for only 72 hours, the single determination revealed a very marked reduction in cerebral oxygen uptake. However, those patients on whom repeated determinations were performed exhibited a further diminution in cerebral oxygen consumption, eventually to extremely low values.

Electroencephalograms recorded on several occasions in cases 1, 2, and 4 showed slow delta activity (3 to 5 per second) of moderate voltage in all leads to either ear without evidence of focal dysrhythmia. The tracings were similar to those reported by others in the course of acute hypoglycemia[2,7,8,11,12], although in our patients the blood sugar levels had been maintained well above normal levels for 2 to 6 days before and during the recording of electroencephalographic tracings. Such post-hypoglycemic electroencephalograms have been described by Proctor and Easton[22] and Halle and Ross[5].

TABLE 1.—CEREBRAL HEMODYNAMICS AND OXYGEN UTILIZATION IN IRREVERSIBLE POST-HYPOGLYCEMIC COMA

Case No.	*Remarks*	*Coma Day*	*CBF*	*MBP*	*CVR*	*A-V O_2*	*CMR O_2*	*A O_2*	*PBS*
1	Female, age 39. Hypoglycemia, 30 mg./100 cc. Survived 3 weeks.	1	74.6	94	1.3	3.62	2.7	11.12	130
		3	62.8	105	1.7	4.41	2.8	10.95	385
		9	56.3	100	1.8	3.51	2.0	8.55	150
			52.4	97	1.8	3.58	1.9	8.63	150
		11	40.9	113	2.8	1.04	.4	14.19	312
			41.8			1.28	.5	13.12	312
2	Male, age 54. Hypoglycemia, 17 mg./100 cc. Survived 2 weeks.	6	75.8	105	1.4	2.33	1.8	8.74	525
		7	49.0	99	2.0	3.03	1.5	8.34	530
		10	26.7	104	3.9	2.69	.7	9.41	850
3	Male, age 48. Hypoglycemia, 35 mg./100 cc. Survived 3 days.	2	61.2	93	1.5	1.66	1.0	15.65	377
4	Female, age 46. Hypoglycemia, 40 mg./100 cc. Survived 1 week.	2	34.9	82	2.3	2.62	1.4	10.23	190
		4	32.9	95	2.9	1.35	.4	8.81	262
		5	47.6	87	1.8	1.43	.6	8.08	230
Mean, All			52.2	99	2.1	2.63	1.5	10.44	358
Controls, range	17 subjects, age 23 to 57, no evident CNS pathology.		42.1 to 81.4	71 to 132	1.3 to 2.7	3.02 to 7.37	2.7 to 4.0	6.52 to 17.07	
Mean, Controls			54.8	106	2.0	6.07	3.3	13.93	

CBF, cerebral blood flow in cc./min./100 gm. brain; MBP, mean arterial blood pressure in mm.Hg; CVR, cerebral vascular resistance in mm. Hg/cc. blood/min./100 gm. brain; A-V O_2, cerebral arteriovenous oxygen difference in volumes/100 cc.; CMR O_2, cerebral oxygen consumption in cc./min./100 gm. brain; A O_2, arterial oxygen content in volumes/100 cc.; PBS, peripheral blood sugar (Folin-Wu) in mg./100 cc.

Comment. It has previously been demonstrated that the depression of cerebral oxygen uptake induced by acute hypoglycemia is not accompanied by any significant change in cerebral blood flow[16]. The progressive diminution in cerebral blood flow seen in 2 of our patients may have been at least in part attendant upon reduction in cardiac output consequent to 1 to 3 weeks

of bed existence; an additional possibility, that of a homeostatic mechanism influencing cerebral blood flow in accordance with chronically reduced metabolic requirements, is only suggested by the gradual increase in cerebral vascular resistance in these 2 patients but can be neither supported nor discounted by the data obtained in so limited a number of subjects.

The striking impairment of cerebral metabolic activity demonstrated in all patients could result only from 1) a diminished metabolite supply (either by reduction of glucose or oxygen concentration in the blood afferent to the brain, or by curtailment of the blood supply itself) or 2) depression of cerebral enzyme systems. In the cases under discussion the arterial sugar and oxygen contents were entirely adequate at the times of study, and in no instance did the cerebral blood flow show a reduction to the extent that the brain would suffer stagnant hypoglycemia or hypoxia. Hence, the remarkably low rates of cerebral oxygen consumption finally observed must by exclusion be attributed to impairment of enzymatic activity. It has been firmly established that the brain obtains its energy practically exclusively from the oxidation of carbohydrate[6,9,10,16,20]; if deprived of this source of energy for an appreciable length of time, the cerebral cells will not only cease to function but may eventually undergo permanent changes in structure leading to irreversibly impaired activity or death[4,14,17,21,23,24,27,28]. Certainly, in our patients the process of permanent cerebral metabolic impairment was at least initiated by undoubtedly prolonged episodes of severe hypoglycemia; it is not unlikely that the situation may have subsequently been aggravated by intermittent periods of hypoxia caused by airway obstruction, so common in deeply comatose patients.

Summary and Conclusions. Cerebral hemodynamics and oxygen utilization were studied at intervals in 4 patients with irreversible post-hypoglycemic coma. The cerebral metabolic rate was moderately to markedly reduced in all subjects and in 3 cases it continued to decrease, eventually reaching extremely low levels. The mean cerebral blood flow showed a marked reduction in only 1 subject, although in 2 others a progressive reduction in flow and increase in cerebral vascular resistance were noted. The significance of these findings is discussed.

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THE USE OF QUINIDINE IN ESTABLISHED AURICULAR FIBRILLATION AND FLUTTER

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In 1914 Wenckebach first noted that auricular fibrillation could be restored to normal sinus rhythm by the use of quinine. However, it was seldom used for this purpose because of its relative ineffectiveness. In 1918 Frey[7] demonstrated that its isomer, quinidine, was much more effective, and in 1921 reported on 50 cases, in 21 of which (42%) normal sinus rhythm was restored. Subsequently several other reports appeared confirming these original observations, but calling attention to the fact that serious accidents such as embolism and sudden death were not uncommon. As a result, the drug tended to fall into disuse.

In 1923 Viko, Marvin, and White[19], as well as many others since then, have not only attempted to determine the incidence of reversion to normal sinus rhythm and its maintenance but also to discover what factors, if any, might influence the response in a given case. The age of the patient, the etiology of the heart disease, the presence of cardiac failure or cardiac enlargement, and the duration of the arrhythmia have all been considered in these studies. In addition, considerable attention has been paid to the incidence of cinchonism, to the more serious toxic arrhythmias that appear, and to the question of sudden death due to quinidine. It is the purpose of this study to reexamine these problems.

Subjects and Methods. Fifty-five patients with auricular fibrillation and 2 with auricular flutter of more than 1 week's duration were treated with quinidine. The duration of the arrhythmia was 1 to 3 weeks in 8, and from months to years in the remaining 49. It was often impossible to determine the exact date of onset even after a careful history. These cases were unselected and were taken serially on admission to the Medical Service which has preponderantly male veterans. Only 2 of the entire group were females. The ages ranged from 25 to 84 years, with the majority (39) in the 5th and 6th decades. Twenty-one patients had rheumatic heart disease, 25 had degenerative heart disease (arteriosclerotic or hypertensive), 2 had cor pulmonale, and 6 had miscellaneous types of heart disease. Three had no demonstrable heart disease. Cardiac enlargement was demonstrated by Roentgen-ray in 43 of the 57 cases, and congestive failure had been present at one time or another in 36. With rare exceptions, failure was well controlled at the time of administration of quinidine.

All but 2 patients received digitalis before quinidine was administered. Other measures for control of congestive failure, such as a sodium-free diet and mercurial diuretics, were utilized as needed. In the large majority, the following dosage schedule was employed: On the first day 0.2 gm. of quinidine was given orally every 2 hours for 7 doses, beginning early in the morning; the individual dose was then increased by 0.1 gm. daily until the patient received 0.5 gm. every 2 hours for 7 doses. The patients were examined several times during the course of each day. If restoration to normal sinus rhythm oc-

curred at any time, the schedule was interrupted and the patient was then placed on a maintenance dose of 0.2 gm. every 6 hours, usually for 1 month or less, following which the medication was discontinued completely. The schedules in a few of the earlier cases differed in that the drug was given generally at 4-hour intervals day and night. It was not considered necessary to give a test dose, and in no case did we encounter true idiosyncrasy which might have been revealed by administering a small preliminary dose. Electrocardiograms were taken once or twice daily beginning on the 2nd day, and more often if ventricular premature beats or QRS widening were noted. The indications for discontinuing therapy before restoration of normal rhythm were: 1) severe symptoms of cinchonism and 2) the development of arrhythmias believed to result from quinidine.

TABLE 1.—CASES OF AURICULAR FIBRILLATION AND FLUTTER TREATED WITH QUINIDINE (REPORTED IN THE LITERATURE 1928–1950)

Authors	*Number of cases*	*% Restored to normal rhythm*
Maynard[15]	53	72
Bramwell and Ellis[4]	27	70
Wolff and White[22]	70	66*
Kohn and Levine[13]	49	71
Berman and Blumenthal[2]	48	31
McMillan and Welfare[16]	50	88
Feigin and Weissman[6]	33	55
Phillips and Levine[17]	53	88.5**
Sokolow *et al.*[12]	15	87
Goldman[8]	48	83
Sokolow and Edgar[18]	30	82
TOTAL	476	
Mean restoration rate		71%

* Cases of severe mitral stenosis and severe congestive failure were excluded in this series.
** No heart disease.

Results. Of the 57 patients, 30 (53%) were restored to normal sinus rhythm. Several previous studies have indicated successful restoration in 31% to 88.5% with a mean of 71% (Table 1). This may be contrasted with an earlier compilation by Burwell and Dieuaide of 606 cases in which the incidence of successful restoration was 56%[5]. The 2 groups together total 1,082 cases with a mean success rate of 67%. The wide variation in the individual reports can be explained by 1) difference in dosage schedules, 2) exclusion of patients with advanced valvular disease or severe congestive failure, 3) inclusion of patients with paroxysmal fibrillation, and 4) inclusion of patients without demonstrable heart disease.

Ten of our patients were given more than one course of quinidine. Two reverted to normal rhythm on the first trial only, 4 reverted on both trials, and 2 failed on both trials. The fact that 2 reverted on the second trial after having failed on the first suggests the

desirability of reinstituting treatment if the fibrillation cannot be controlled otherwise.

The dosage of quinidine in those patients successfully restored and in those who failed to revert has been compared in Table 2. In the latter, the average total dosage was 6.1 gm. over a period of 3.1 days, as contrasted with 3.8 gm. for 2.4 days in those successfully restored to normal sinus rhythm. More significant, perhaps, is the fact that those reverted required an average of 1.6 gm. per day, whereas those who failed did so despite the larger dose of 2.0 gm. per day. This finding is essentially in agreement with that of Sokolow and Edgar[18], who came to the conclusion that if restoration to sinus rhythm did not occur with moderate doses and moderate blood quinidine levels, higher doses were only infrequently successful. It must be emphasized that in the large majority of our cases, the total daily dose was crowded into a period of 12 hours, and therefore higher blood quinidine levels were probably obtained for that portion of the day than for a similar dose spread over 24 hours.

TABLE 2.—EFFECT OF QUINIDINE DOSAGE, HEART SIZE, AND CARDIAC DECOMPENSATION ON RESTORATION RATE

	Total Cases	*Average Total Dose of Quinidine, gm.*	*No. of Days Adm.*	*Average in gm./day*	*Cardiomegaly*		*Decompensation*	
					No.	*%*	*No.*	*%*
Restored to normal rhythm	30	3.8	2.4	1.6	19	63	16	53
Failed	27	6.1	3.1	2.0	24	89	20	74

The presence of cardiac enlargement may have some significance with regard to successful therapy (Table 2). Of the 30 cases restored to normal sinus rhythm, 63% had cardiac enlargement, whereas of the 27 failures, 89% had enlargement, suggesting that the presence of this abnormality might operate against successful therapy. This is contrasted with the experience of Wolff and White[22], who stated that the degree of enlargement appears to have no influence on the success of therapy.

The history of cardiac failure at one time or another was also somewhat unfavorable. Among the cases restored to normal sinus rhythm, 53% gave a history of decompensation, whereas a similar history was obtained in 74% of the failures. Frey in 1921 noted that he was able to restore to sinus rhythm 66% of the compensated cases and only 31% of the decompensated[7]. This difference has been repeatedly confirmed[15,19,22].

Of the patients with degenerative heart disease, 64% were successfully restored to normal rhythm, as contrasted with only 38% of the rheumatic group, despite the fact that the former was an older age group than the latter. The remaining etiologic groups listed in Table 3 were too small to be of any statistical significance. There is considerable difference of opinion in the literature concerning the influence of etiology. Some authors found that it was of little or no significance[10,19,22]. Others concluded that patients with rheumatic heart disease were restored more easily[16], whereas in another series, as in ours, it was noted that patients with degenerative heart disease responded more readily[12]. Kalmansohn and Sampson[12] reported that the plasma quinidine content at the time of reversion to

normal rhythm ranged between 7.48 and 23.7 mg. per liter for 6 patients in the rheumatic group, and between 3.30 and 5.67 mg. per liter for 6 in the degenerative group.

Despite careful histories, we found that it was quite difficult to elicit the exact time of onset of the arrhythmia except in a general way. This was particularly true of those in whom the arrhythmias had been present for many months or years. We are therefore unable accurately to correlate this factor with the incidence of successful therapy. However, most reports indicate that it is much more difficult to terminate an arrhythmia of long duration[7,15,19,22].

TABLE 3.—ETIOLOGY OF THE HEART DISEASE CORRELATED WITH RESTORATION RATE

	Rheumatic		*Degenerative*		*Cor Pulmonale*		*No Heart Disease*		*Other Disease*	
Result	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
Restored to normal rhythm	8	38	16	64	1	50	3	100	2	33
Failed	13	62	9	36	1	50	0	0	4	67
TOTAL	21		25		2		3		6	

Twenty-eight of the 57 patients in this series (49%) experienced symptoms of cinchonism, but in only an occasional case was it necessary to discontinue the drug for this alone. Anorexia, nausea, vomiting, and diarrhea appeared either after the first day or following moderately high doses. These were the most common symptoms and were experienced by 40% of the patients. Tinnitus, vertigo, drowsiness, incoordination, and confusion were experienced by only 5 patients (9%), and these manifestations were much more specifically correlated with high doses or long continued therapy. It is generally believed that symptoms of cinchonism are common but not serious, and unless severe do not of themselves contraindicate continuation of therapy[9,13,16,19]. We encountered no episodes of syncope, convulsions, collapse, or respiratory difficulty that might have been considered drug idiosyncrasy.

Acquired sensitivity to the drug occurred in 2 patients. One developed petechial hemorrhages over both legs 1 week after quinidine was discontinued, and another developed an acute exfoliative dermatitis while on maintenance doses. The former disappeared gradually, and the latter cleared promptly on discontinuing the drug.

In attempting to correlate plasma quinidine levels with toxic manifestations, Kalmansohn and Sampson[12] found that gastrointestinal irritability is not related to plasma concentration and therefore probably represents a local effect of the drug on the gastrointestinal tract. On the other hand, symptoms associated with the central nervous system, such as giddiness, tinnitus, and visual disturbances, as well as marked fall in blood pressure, seem to occur at higher quinidine levels. Their only reasons for discontinuing the drug were extreme malaise, ventricular arrhythmias, and significant fall in blood pressure.

Significant changes in the electrocardiogram are encountered during quinidine therapy. It has long been known that one of the most characteristic effects of the drug is that of slow-

ing of auricular impulse formation. In the present series the average auricular rate at the height of quinidine therapy was 268 for the successfully treated cases just prior to restoration, and 245 for the failures. The only significance that may be attached to this difference is that the quinidine dosage in the latter group was higher (Table 2). Many of the cases which revert to normal sinus rhythm abruptly may show little or no slowing, but all those which require moderate to large doses demonstrate a decrease in the auricular rate from 450 to 550 ("fibrillation") to 180 to 300 ("flutter"). At lower rates there is a definite tendency to a regular ventricular response, usually 2:1 to 4:1. On physical examination this may at times be mistaken for reversion to normal sinus rhythm. Two patients experienced the unfortunate phenomenon of 1:1 response at rates of 220 and 260, despite adequate digitalization. The slowing of the auricular rate has been utilized in estimating the extent of quinidine effect and correlated with serum quinidine levels[14,18]. Wégria[20], however, in observing the maximum effect of a single dose, found that the extent of the fall in the circus rate varied from patient to patient and that it was not always proportional to the size of the dose. Ordinarily, on discon-

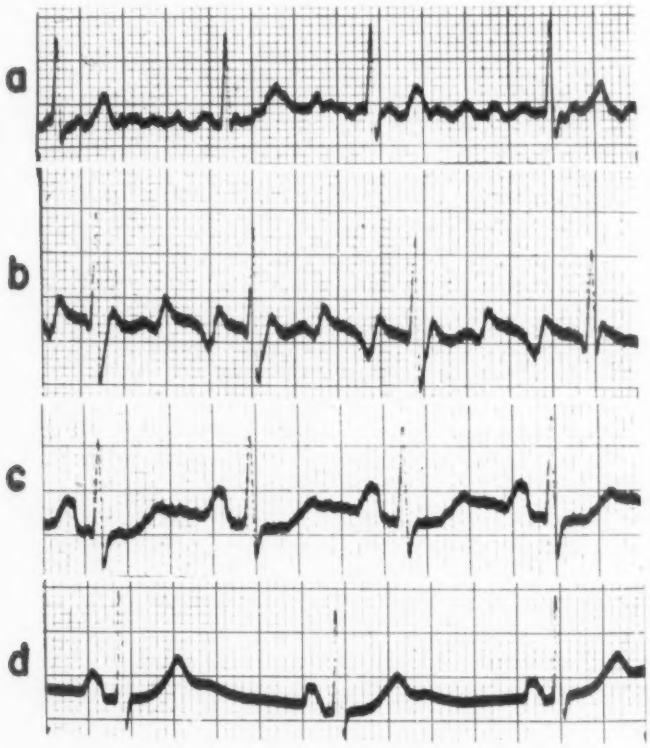

FIG. 1.—Lead II. W. J. M. a) 11/22/50: Auricular fibrillation. b) 11/29/50: Auricular flutter with regular 3:1 response; auricular rate, 240; ventricular rate, 80; considerable widening of QRS. c) 11/30/50: Normal sinus rhythm after 9.8 gm. of quinidine given over a period of 4 days; marked enlargement of P waves. d) 1/9/51: Normal sinus rhythm; size of P waves and width of QRS complexes are diminished.

tinuing quinidine in the cases which failed to revert to normal sinus rhythm, the auricular rate increased to 450 to 550 within 48 hours, at which time the original state of auricular fibrillation was once more present. However, in 2 patients flutter continued to be present for about 7 to 10 days. This has been noted occasionally by others and has been referred to as "fixed flutter"[8,19].

The depressant effect of quinidine is evidenced not only by its impairment of impulse formation in the auricle, but also by slowing of ventricular conduction time. Slight widening of the QRS complex (less than 25%) is a common finding if carefully searched for. It was noted in 22 of our 57 cases. Widening greater than 25% was seen in only 9 cases (including 2 of bundle branch block) and is a contraindication to further therapy except in desperate situations.

The broad notched P waves that are present in many of the cases successfully restored to normal sinus rhythm are analogous to the QRS widening. This was noted in 12 of the successfully treated patients, excluding the patients with mitral stenosis. Slight prolongation of the P–R interval has also been reported as one of the depressant effects of this drug. Some of the elec-

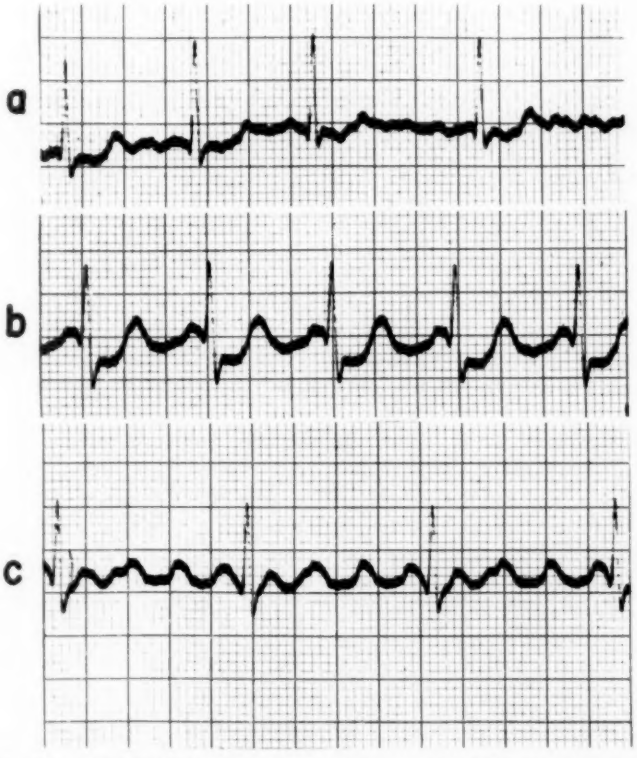

FIG. 2. Lead II. C.P. a) 10/24/50: Auricular fibrillation. b) 10/26/50: Auricular flutter with regular 2:1 response after 6.3 gm. of quinidine given over a period of 3 days; auricular rate, 210; ventricular rate, 105; slight widening of QRS. c) 10/27/50: Auricular flutter with regular 4:1 response; auricular rate, 270; ventricular rate, 68. This patient failed to revert to sinus rhythm.

trocardiographic changes commonly seen in conjunction with the use of quinidine are illustrated in Figs. 1 and 2.

Quinidine may also be a myocardial irritant. Although this effect usually occurs with large doses, this is not always true. In one case it occurred following 2.6 gm. given over a period of 2 days. Runs of ventricular premature beats may be the first warning; when these appear the drug should be discontinued immediately. Ventricular tachycardia has often been considered a rare complication, but in a series of 65 patients treated with quinidine (including the 57 cases herein reported), 6 developed this serious arrhythmia[21].

Of the 30 patients restored to normal rhythm, follow-up data are available in 28. Fourteen continued in normal rhythm for periods of from 2 to 16 months, the average being 6 months. Thus only 14 of the original 57 cases (25%) were restored to normal rhythm and so maintained for an average follow-up period of 6 months. This corresponds quite well with the reports of others (summarized in Table 4). It is of some interest that 10 of these had cardiac enlargement or a history of decompensation, or both, suggesting that these factors need not prevent successful maintenance of normal sinus rhythm. The desirability of continuing patients on maintenance doses of quinidine has not been fully determined. With a rare exception, none of our patients was continued on the drug for more than 1 month.

TABLE 4.—MAINTENANCE OF NORMAL RHYTHM FOLLOWING RESTORATION

	Total Cases	*Restored to Normal Rhythm and Maintained*	*Follow-up Period*
Viko, Marvin and White[19]	?	33%	Not given
Burwell and Dieuaide[5]	16	38%	6 months
Maynard[15]	53	28%	6 months
Bramwell and Ellis[4]	27	33%	24 months
Harris[10]	43	35%	6 months
Kohn and Levine[12]	49	36%	12 months
Berman and Blumenthal[2]	48	31%	14 months
McMillan and Welfare[16]	50	28%	4–24 months
Holzman and Brown*	57	25%	2–16 months (average = 6 months)

* Present series.

Discussion. The ultimate success of quinidine therapy depends on how many patients can be maintained in normal rhythm, and on the benefits to be derived from that rhythm. The factors which influence the duration of successful maintenance have been described by Phillips and Levine[17]. They found that patients under 50 years of age, those whose arrhythmias have been present for less than 1 year, and those with no evidence of organic heart disease tend to remain in normal rhythm for longer periods of time. On the other

hand, in the present series, 10 of the patients who were maintained did have evidence of organic heart disease, and possibly of long continued fibrillation.

The benefits to be derived from normal sinus rhythm are 1) slower ventricular rate[3,4,22] and 2) prevention of peripheral embolism occurring on the basis of thrombus formation in a dilated auricle. Digitalis certainly does not always control the ventricular rate in fibrillators, especially during exertion[3,4], whereas some of the patients restored to sinus rhythm do much better[22]. Whether or not the presence of normal rhythm will prevent thrombus formation and peripheral embolism has not as yet been clearly established. Not uncommonly the appearance of this accident is merely coincident with the use of the drug rather than the result of it[1,4,19,23] and it is believed by some that even with restored sinus rhythm the dilated auricle remains unchanged, contracts poorly, and therefore continues to be a source of emboli. On the other hand, a series such as that reported by Hay[11], in which there were 6 instances of peripheral embolism among 147 successfully treated cases, is somewhat discouraging. These accidents occurred from 3 hours to 4 days following the appearance of sinus rhythm.

In addition, other dangers in the use of quinidine must be taken into consideration. Sudden death associated with cardiac asystole, respiratory arrest, or collapse has been reported on rare occasions due either to the marked depressant effect of the drug or to idiosyncrasy. There is no way of predicting these accidents.

Although virtually all of our cases were digitalized prior to quinidine therapy, it has been suggested that at least some may be restored more easily without digitalis. The chief reason for its use aside from cardiac failure is to prevent the paradoxical increase in ventricular rate that may be encountered when the auricular rate has been slowed to 200 to 250. Digitalis, by its effect on slowing conduction through the AV node, is thought to prevent a 1:1 response. However, 2 patients in the present series developed this situation despite full digitalization.

In the final decision as to whether or not quinidine should be used, all of the above-mentioned factors must be considered.

Summary. 1. Fifty-five unselected patients with established fibrillation and 2 with established flutter were treated with quinidine in the attempt to restore normal sinus rhythm. The large majority were in their 5th or 6th decades and had either rheumatic or degenerative heart disease.

2. Thirty (53%) were successfully restored to normal rhythm, but only 14 (25%) were so maintained over an average follow-up period of 6 months.

3. The factors which operate against successful restoration are a) long duration of the arrhythmias, b) the presence of cardiac enlargement or a history of cardiac failure, and c) the presence of rheumatic heart disease.

4. Those patients who revert to normal rhythm usually do so with moderate doses of the drug. At times, however, a second attempt is successful when the first has failed.

5. Symptoms of cinchonism are common and occurred in half of the patients in this series. Only occasionally were they severe enough to necessitate discontinuing the drug. None of the manifestations of idiosyncrasy (collapse, respiratory embarrassment, or sudden death) were encountered.

6. The significant electrocardiographic changes were: a) slowing of auricular impulse formation, with a

tendency to regular ventricular response, b) increase in intraventricular conduction time, c) increase in intra-auricular conduction time in those cases which were restored to normal rhythm (enlargement of the P waves), and d) evidence of ventricular irritability.

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INDUCED INTERMITTENT CLAUDICATION*

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Pain in the legs is the chief symptom of arteriosclerosis obliterans of the lower extremities and the one which most frequently causes the patient to seek medical attention. Wright[13] lists 2 main types, the pain of intermittent claudication and pain at rest. Although the presence of intermittent claudication correlates well with the degree of ischemia, there is still debate as to the nature of rest pain. Wright[13] feels that the cramp-like pains which occur while the patient with arteriosclerosis is in bed are associated with ischemia in the majority of cases, while Allen, Barker, and Hines[1] are of the opinion that this symptom is usually not related to ischemia.

Many tests have been devised to produce intermittent claudication and to measure claudication time. Barker, Brown, and Roth[2] had the patient walk at 120 steps per minute until claudication was produced. Simmons[9] used a pedal ergometer with the rate of contraction controlled by a metronome set at 60 beats per minute, while Landis *et al.*[5] employed a similar technique, using faradic current to initiate muscular contraction. A foot treadle ergometer was used by Fisher, Duryee, and Wright[3] on which the patient pressed down at the rate of 120 times per minute until claudication was produced. Kissen[6] adapted the Master 2-step test for the measurement of claudication time. The number of trips the patient made, the time of onset of pain, and the amount of time necessary for the pain to subside were recorded. Although the bicycle ergometer has been used for physiological studies[4,12], it has not been used to produce claudication. It seemed worth while[10] to ascertain whether or not claudication could be produced on a bicycle ergometer in patients with arteriosclerosis obliterans of the lower extremities. We intended also to develop the procedure as a quantitative clinical measurement to evaluate effects of vasodilator drugs[11].

Subjects and Methods. Twenty-nine hospitalized male patients were studied for the presence of cerebral, retinal, cardiac, renal, and peripheral arteriosclerosis by history and by clinical and laboratory examinations, special emphasis being placed on the status of the blood vessels using accepted methods[7,13]. The patients were questioned specifically for the symptoms of intermittent claudication and night cramps. A history of the use of tobacco and alcohol was obtained. The fundi were carefully examined and the presence of arteriosclerotic and hypertensive changes evaluated according to the Keith-Wagener classification. Roentgenograms of the chest and legs and 12-lead electrocardiograms

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were made. Oscillometric readings using the Boulitte oscillometer were recorded.

A friction belt bicycle ergometer with the 5-pound weight was used. All tests were run at a rate of 72 half cycles per minute regulated by a metronome. The patients were instructed to pedal the bicyle with the ball of the foot for 10 minutes or until they developed claudication, that is, pains or cramps in the legs. Little difficulty was encountered in differentiating intermittent claudication from other pains in the extremities. Transient pains were noted in several patients, but these disappeared with continued exercise. In contrast, the development of pain or cramps which forced the patient to stop abruptly were considered to be claudication. If angina or severe dyspnea developed, the test was stopped. The time necessary to produce pain was noted by an observer with a stop watch. If claudication could not be produced within 10 minutes, the test was considered negative. Eighty-three exercise tolerance tests were done on the 29 patients. Two tests were carried out 15 minutes apart at semi-weekly intervals.

The patients were divided into 3 groups. Group 1 consisted of 9 patients without clinical manifestations of arteriosclerosis. None of these had a history of intermittent claudication, although 2 had a previous history of night cramps. Their ages ranged from 36 to 67 with a mean of 47.4 years. Group 2 consisted of 11 patients with signs of arteriosclerosis involving the cerebral, retinal, cardiac, and renal vessels, either singly or in combination, but without symptoms or signs of arteriosclerosis obliterans of the lower extremities. No one in this group had previous intermittent claudication or night cramps. Ages ranged from 41 to 68 with a mean of 55.8 years. Group 3 consisted of 9 patients with symptoms and signs of obliterating arteriosclerosis of the peripheral vessels. Some of these had evidence of arteriosclerosis elsewhere. All had a history of intermittent claudication and 4 also complained of rest pain, usually cramp-like pains at night. Their ages ranged from 44 to 72, with a mean of 60.4 years.

Results. Sixteen exercise tolerance tests were performed on the 9 patients in Group 1. None developed intermittent claudication, although 2 patients (Cases 12, 26) had pains in the legs following exercise. The tests on the other 7 patients were entirely negative (Table 1). We do not think that the symptoms of the two patients (Cases 12, 26) who developed pains in the legs following exercise could be termed intermittent claudication. In Case 12, the patient, a 50-year old Negro with marked luetic aortic insufficiency, noted a "tired sensation" in both legs without cramps and the test was discontinued at 190 seconds due to the development of severe dyspnea. In Case 26, the patient, a 37-year old white male with rheumatic heart disease and probable rheumatic activity, developed a slight cramp in his left thigh and calf at 453 seconds, which was similar to the night cramps he had noted for several years. Vague "growing pains" in his legs were a prominent part of his rheumatic history for the previous 12 years. It is of interest that in Case 9, the patient, a 67-year old man with rheumatoid arthritis and macrocytic anemia, exercised for 10 minutes without symptoms. Roentgenograms of his legs showed marked "pipe stem" calcification of the arterial walls, although there were no other signs of arteriosclerosis. His hemoglobin was 6.5 gm. at that time. The other 8 patients had no signs of arteriosclerosis by physical examination or Roentgen-ray examination.

Twenty-two tests were done on the 11 patients of Group 2 and in no instance could claudication be produced. One patient (Case 30) developed angina and 5 patients (Cases 14, 20, 21, 34, and 35) developed sufficient dyspnea so that the tests were stopped somewhat short of 10 minutes. Oscillometric readings were all normal and only one patient (Case 34) showed evidence of calcification of the arterial walls of his legs. He was a 67-year old white male with hypertensive and arteriosclerotic heart disease and slight left hemiparesis as a residue from a cerebral vascular accident in 1944. One

TABLE 1.—CLINICAL DATA AND RESULTS OF ATTEMPTS TO PRODUCE CLAUDICATION WITH BICYCLE ERGOMETER IN 29 PATIENTS

Case No.	Diagnosis*	Age	Color	Classification Group	Claudication	Night Cramps	Sites of Arteriosclerosis†	Calcification of Vessels of Legs	No. of Exercise Tolerance Tests	Results: Claudication	Results: Dyspnea	Results: Angina	Time of Exercise in Seconds: Range	Time of Exercise in Seconds: Mean
1	Diabetes, ASO	72	W	III	+	+	Rt Cd Pr	0	9	+	0	0	45–95	55
4	Hypothyroid AS, ASO, Hypertension	63	W	III	+	+	Pr	+	8	+	0	0	103–170	135
5	Bronchiectasis, Rh. Arth.	54	W	I	0	0	None	0	2	0	0	0	480–600	540
6	ASHD, HCVD, GAS, ASO	68	W	III	+	+	Cr Rt Cd Rn Pr	—	2	+	+	0	100–115	107
7	HCVD, duod. Ulcer.	41	W	II	0	0	Rt Cd	0	2	0	+	0	600–600	600
8	ASHD	61	N	III	+	+	Rt Cd Rn Pr	0	10	+	+	0	75–331	161
9	Rh. Arthritis	67	W	I	0	0	None	+	1	0	0	0	600	600
11	Periarteritis	53	W	III	+	0	Rt Cd Rn Pr	0	1	+	+	0	204	204
12	Luetic HD	50	N	I	0	0	None	0	3	+	+	0	179–205	190
14	HCVD, Uremia, DM, Anemia	55	W	II	0	0	Rt Cd Rn	0	1*	0	+	0	121	121
15	Bronchiectasis, Cirrhosis	46	W	I	0	0	None	0	1	0	0	0	600	600
17	ASHD, DM, ASO,	44	W	III	+	0	Rt Cd Pr	+	6	+	0	0	44–63	57
18	Osteoarthritis, Cirrhosis, GAS	70	W	III	+	0	Rt Pr	+	3	+	+	0	89–180	138
19	Cirrhosis, Hypertension	50	W	III	+	0	Pr Rt	0	4	+	0	0	45–82	67
20	ASHD, Polycythemia vera	56	W	II	0	0	Cd	0	2	0	+	0	400–540	470
21	Luetic HD, HCVD	61	N	II	0	0	Cd	—	2	0	+	0	124–372	248
22	Cirrhosis	36	W	I	0	+	None	—	2	0	0	0	600–600	600
23	Tabes, Arthritis	50	W	I	0	0	None	0	2	0	0	0	300–600	450
24	ASHD, Lues	60	W	II	0	0	Cr Rt Cd	0	4	0	0	0	600–600	600
26	RHD, Rh. fever	37	W	I	0	+	None	—	2	+	0	0	416–490	453
27	ASHD,	63	W	III	+	0	Rt Cd Pr	—	2	+	+	0	189–270	220
28	Asthma, Cor Pul. ASHD	51	W	II	0	0	Cd Rt Rn	0	2	0	0	0	600–600	600
29	Portal cirrhosis	41	W	I	0	0	None	—	2	0	0	0	600–600	600
30	HCVD,	46	W	II	0	0	Rt Cd Rn	—	2	0	0	+	151–390	270
31	HCVD, ASHD	68	W	II	0	0	Rt Cd	0	2	0	0	0	600–600	600
32	Cirrhosis	46	W	I	0	0	None	0	1	0	0	0	600	600
33	Rh. Arthritis, Chr. Neph.	52	W	II	0	0	Rt Cd-Rn	0	1	0	0	0	600	600
34	HCVD, ASHD	67	W	II	0	0	Cr Rt Cd Rn	+	2	0	+	0	240–310	275
35	HCVD, ASHD, Silicosis	57	W	II	0	0	Cd	0	2	0	+	0	420–432	426

*ASO = Arteriosclerosis obliterans
*GAS = General Arteriosclerosis
*ASHD = Arteriosclerotic Heart Disease
*HCVD = Hypertensive cardiovascular disease
*DM = Diabetes mellitus
*RHD = Rheumatic Heart Disease

†Cr = Cerebral
†Rt = Retinal
†Cd = Cardiac
†Rn = Renal
†Pr = Peripheral

patient (Case 30), a 46-year old Puerto Rican male with hypertensive cardiovascular disease, developed anginal pain after 270 seconds. He was the only patient in the entire group who developed angina, although 8 patients (Cases 6, 7, 12, 14, 20, 21, 30, and 34) had a past history of anginal pain.

Forty-five tests were performed on the 9 patients in Group 3 and in every case claudication was produced, usually within 90 seconds. Four patients in this group had a history of night cramps, and one (Case 4) had a healed arteriosclerotic ulcer on his right ankle. Pulsations were present in 3 patients (in Cases 1, 7, and 11). In Case 2 no pulsations were present below the right femoral artery, and in the remaining 5 cases (6, 17, 18, 19, and 27) the posterior tibial pulsations were absent in 4 (all except Case 6) and the dorsalis pedis pulsations were absent in 2 (Cases 6 and 27). All patients showed marked pallor on elevation and marked rubor on dependency. Oscillometric readings were low or absent with two exceptions (Cases 8 and 19). Roentgenograms of the legs (AP and lateral exposures) were made for 7 patients and only 3 (Cases 4, 17, and 18) showed evidence of calcification of the arteries. Intermittent claudication was produced in every instance. The claudication times were reproducible for each patient. The end points were sharp in every case but one (Case 18). The shortest claudication time was 44 seconds (Case 17) and the longest was 331 seconds (Case 8), while the mean for the group was 114 seconds (Table 2).

TABLE 2.—RESULTS OF ATTEMPTS TO PRODUCE CLAUDICATION IN 9 PATIENTS WITH ARTERIOSCLEROSIS OF EXTREMITIES

Case Number	*Age*	*Claudication Time in Seconds Initial Time*	*Claudication Time: Repeated After 15 minutes*	*Mean Value for Single Day*	*Mean for All days*
1	72	60	55	57	
		45		45	
		60	95	77	
		52	48	50	
		45	50	47	55
4	63	120	160	140	
		140	170	155	
		103	120	111	
		126	144	135	135
6	68	100	115	107	107
8	61	75	77	76	
		120	125	122	
		130	83	106	
		331	232	281	
		280	157	218	161
11	53	204		204	204
17	44	44	58	51	
		60	56.5	58	
		63	63	63	57
18	70	90		90	
		144*		144	
		180*		180	138
19	50	77	82	79	
		66	45	55	67
27	63	189	270	220	220

* Poor end point

Discussion. Several conclusions can be drawn from these studies. There appears to be a good correlation between the history of intermittent claudication and clinical evidence of obliterating arteriosclerosis. While night

cramps are less frequent in peripheral arterial disease than is intermittent claudication, the history of frequent night cramps should call for a complete vascular examination.

The degree of arterial calcification as shown by Roentgen-ray examination is not clearly related to the state of the circulation. Five patients had Roentgen-ray evidence of calcification in the legs. Two had no evidence of arterial insufficiency, while 3 had the clinical manifestations of obliterating arteriosclerosis.

All of the various methods used for the production of intermittent claudication have limitations. Extensive studies have been made using the Landis passive ergometer. These studies[8] have proved unsatisfactory because of the pain induced by the stimuli, the stimulation of antagonistic muscle groups, and the demonstrable errors due to psychological factors. All foot pedal ergometers test only a single extremity at a time, and while this may be of value in comparing the 2 legs, we think that it is more desirable to use a simultaneous bilateral test, as this more closely simulates the natural development of intermittent claudication.

Summary. 1. The induction of intermittent claudication using the friction belt bicycle ergometer is described.

2. Good correlation was found between clinical evidence of arterial insufficiency in the legs and induced claudication.

3. The exercise tolerance test is no better than a good history and clinical examination in the diagnosis of obliterating peripheral arteriosclerosis. All patients in whom claudication could be produced had a previous history of intermittent claudication.

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ELECTROCARDIOGRAPHIC CHANGES IN POLIOMYELITIS*
ANALYSIS OF 150 CASES

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The electrocardiographic changes occurring in children during the acute phase of poliomyelitis with a brief review of the literature up to 1949 were reported in a previous communication[2]. Since then, Spain *et al.*[4] have shown the pathological evidence of myocarditis in many cases of poliomyelitis. Weinstein and Shelokov[6] in a recent publication have stressed the cardiovascular manifestations in patients with acute poliomyelitis. In their series, abnormal findings in the electrocardiograms were observed in more than 25% of the patients. The present study was undertaken to show abnormal electrocardiographic changes in both children and adults admitted to the Strong Memorial and Rochester Municipal Hospitals during the period between July and November, 1950.

Method and Material. Techniques employed in the study of patients admitted in 1950 were very similar to those used in 1949 which were described in detail[2]. Electrocardiograms of 12 leads (3 standard limb, 3 unipolar limb, and 6 unipolar precordial) were recorded with a direct writing machine and a total of 696 electrocardiograms was taken. The initial tracings were usually taken within 24 hours of admission and frequently repeated at 2 to 4 day intervals. After the first 2 weeks, follow-up studies were made on 93 patients with abnormal electrocardiographic findings.

Criteria for normalcy in children are based on the recent study by Yu, Joos, and Katsampes[9]. Normal standards for adults are taken from the paper published by Sokolow[3] and also from our unpublished data[8]. The QT interval was determined from measurements on the longest and shortest cycle in each of 6 leads. The average of these readings was then used for the computation of corrected QT interval (QT_c); $QT_c = \frac{QT\ (\text{seconds})}{\sqrt{NR-R\ (\text{seconds})}}$, by the application of a modification of Bazett's formula[5]. In all individuals the upper limit of QT_c was 0.43 and the lower limit 0.38.

There were 100 children whose ages varied between 4½ months and 14 years, and 50 adults, the oldest of whom was 39. The sex distribution was practically equal in both children and adults.

Results. ABNORMALITIES IN THE TOTAL SERIES OF 150 CASES. Only 9 adults and 25 children had completely normal tracings throughout the study. The type and distribution of abnormalities found in the remaining 116 cases are described as follows:

1. *Rate* (Table 1). Sixty-two patients had sinus tachycardia and 6 sinus bradycardia. Most instances of tachycardia occurred early in the illness, usually during the febrile period.

2. *Rhythm.* Seven individuals demonstrated transient arrhythmias, consisting mainly of premature contractions.

* This study was aided by grants from the Helen Hay Whitney Foundation and the Hochstetter Fund.

3. *P Waves.* No abnormalities of the P Waves were noted in this series.

4. *P-R Interval.* Three patients showed prolongation of P-R interval.

5. *QRS Complex.* Low voltage of the QRS complex in Leads V_{1-3} was encountered as a transient, isolated finding in 1 child. Low voltage of QRS in V_6 occurred in one adult who later developed a prolonged QT_C. Low voltage of QRS in all precordial leads appeared in one adult.

6. *Ventricular Hypertrophy and Strain.* Evidence of right ventricular hypertrophy was present in only one adult. Three children had abnormally high R waves and low or absent S waves in V_1, suggesting right ventricular hypertrophy. Left ventricular strain was a transient abnormality in one child. Evidence of left ventricular hypertrophy was demonstrable in one adult.

7. *RS-T Segment.* In 2 children depression of the RS-T segment was present.

8. *T Waves.* The abnormalities of T waves encountered in 65 patients are summarized in Table 1. High, peaked T waves occurred in 10 patients and low or diphasic or inverted T waves were present in 55 patients. These changes were transient in all individuals.

9. *QT Interval.* The last section in Table 1 shows the number of cases with short and prolonged QT interval. Eighteen adults and 27 children had prolonged QT_C, whereas 1 adult and 4 children showed short QT_C.

RELATION OF ELECTROCARDIOGRAPHIC FINDINGS TO CLINICAL DATA (Table 2).

1. *Duration of Fever.* No significant correlation between duration of fever and electrocardiographic abnormalities could be determined.

2. *Duration of Illness.* Over 75% of the patients showed their initial changes during the first 2 weeks of illness. The majority of these had reverted to normal by the end of the first month, and comparatively only a small number of patients had persistent changes thereafter. Several patients still showed abnormalities 3 months after the onset of disease. A prolonged QT_C was most commonly encountered in these late follow-up tracings. T wave abnormalities tended to appear earliest and often preceded QT_C prolongation in a given individual. Other abnormalities such as arrhythmias,

TABLE 1.—SUMMARY OF IMPORTANT ABNORMAL FINDINGS IN 116 CASES OF POLIOMYELITIS

Abnormality	*With No Other Abnormality*		*With Other Abnormalities*		*Totals*		*Combined*	
	Adults	*Children*	*Adults*	*Children*	*Adults*	*Children*	*No.*	*%*
Rate								
Tachycardia	5	14	18	26	23	40	63	42
Bradycardia	0	2	3	1	3	3	6	4
PR Interval								
Prolonged	0	0	0	3	0	3	3	2.0
T Waves								
Diphasic Inverted, or Low voltage	4	6	16	29	20	35		
High, peaked	3	2	5	0	8	2	65	43.3
QT Interval								
Short	1	1	0	3	1	4		
Prolonged	3	4	15	23	18	27	50	33.3

prolonged P-R interval, and low voltage of QRS had their onset over a longer period of time.

3. *Type of Poliomyelitis, Severity of Paralysis, and Age of Patient.* An attempt was made to correlate the type and severity of illness with the electrocardiographic findings. For this purpose the series was divided into 2 groups. The first comprised 69 individuals with normal or borderline electrocardiograms, and the second included the remaining 81 patients with definitely abnormal tracings. These groups were then compared from the point of view of number of tracings taken, age of patient, duration of fever, type of poliomyelitis, and extent of paralysis. The extent of paralysis was arbitrarily classified from O, representing non-paralytic, to + + + + +, indicating fatal cases. The intermediate signs from + to + + + + indicated increase in severity from cases with minimal paralysis to those with paraplegia. The results appear in Table 3. They suggest that adults as well as individuals with bulbar or high cervical paralysis are more prone to electrocardiographic abnormalities than those with other types of paralysis. The 2 respirator patients, both adults, who

TABLE 2.—ONSET OF ELECTROCARDIOGRAPHIC ABNORMALITIES IN RELATION TO DURATION OF ILLNESS

Abnormality	*1st Week*	*2d Week*	*3d Week*	*4th Week or Later*
T Waves				
No. of Cases	47	12	5	1
%	72	18.5	8	1.5
QT Interval				
No. of Cases	33	19	7	5
%	51.5	30	11	7.5
Others (Excluding Tachycardia)				
No. of Cases	11	5	2	3
%	52.5	24	9.5	14

TABLE 3.—COMPARISON OF CLINICAL DATA WITH ELECTROCARDIOGRAPHIC ABNORMALITIES

	Normal or Borderline Electrocardiograms	*Abnormal Electrocardiograms*
Average Number of Tracings	2.77	3.3
No. of Patients		
Children	51	49
Adults	18	32
Total	69	81
Extent of Paralysis*		
0	22	17
+	14	18
+ +	18	17
+ + +	10	17
+ + + +	3	9
+ + + + +	2	3
Bulbar or High Cervical Paralysis	20	44
Average Duration of Fever in Days	4.23	5.3

* See Text for Explanation

survived to a prolonged convalescence with persistent electrocardiographic abnormalities, illustrate this point. However, in any given case clinical information is of little value for accurate prediction.

4. *Serum Potassium and T wave Changes.* An elevation of serum potassium has been shown to produce high, peaked T waves in the electrocardiogram[1,7]. Since electrolyte imbalance is possible in patients severely ill with poliomyelitis or those receiving frequent hot packs, serum sodium and potassium determinations were made on 75 children and 6 adults during the acute phase of illness. The results were then compared with T wave changes (Table 4). Of the 11 patients with serum potassium levels higher than 6 mEq./L., only 2 had high T waves in the precordial leads. Of 8 cases with similar T wave changes, only 1 could be suspected of having abnormal electrolytes, 3 had proved normal potassium, and 4 were ambulatory convalescents. These results indicate that although an elevated potassium level in the serum may cause high, peaked T waves, the latter may also occur with a normal serum potassium level.

TABLE 4.—COMPARISON OF T WAVES IN THE PRECORDIAL LEADS WITH SERUM POTASSIUM LEVEL IN 75 CHILDREN AND 6 ADULTS

Serum Potassium Level	*T Waves*	*Number of Cases*
Normal		
4.32 to 5.92 mEq. L.	Normal	67
	High, peaked	3
Elevated		
6.14 to 6.84 mEq. L.	Normal	8
	High, peaked	1
Greater than 7.00 mEq. L.	Normal	1
	High, peaked	1
No Potassium Determination	High, peaked	4 convalescents 1 acutely ill

5. *Clinical Carditis.* All patients were checked for any evidence of preexisting cardiac pathology by means of history and physical and roentgenologic examinations, and negative findings were obtained in 136 individuals. Eight patients had apical systolic murmurs considered to be of functional origin and 2 additional patients gave slight Roentgen-ray evidence of cardiac enlargement. Since all the 10 patients had normal electrocardiograms at some time during the study, the physical and roentgenological findings were probably unrelated to the poliomyelitis. Two children with incompletely diagnosed congenital cardiac lesions also had normal electrocardiograms. Of the total 136 patients admitted with negative cardiac findings, only 6 subsequently developed clinical evidence of carditis. In each case there were transient arrhythmias, confirmed by electrocardiograms in 5. Four of these 6 patients subsequently died. Of the remaining 2, one was an adult with moderately severe poliomyelitis, the other a child with mild disease. All 6 had bulbar involvement.

6. *Histological Findings.** There were 8 fatal cases in the 1950 epidemic and all had complete autopsies. One or more electrocardiographic tracings were obtained during the course of illness in 6 patients, 5 of whom showed abnormal changes. Evidence of marked pulmonary congestion and edema was shown in 5 cases, pulmonary infarction and emboli in 2, bronchopneumonia in

* We are indebted to Dr. William B. Hawkins and Dr. Stanley B. Troup of the Department of Pathology for the pathological examination.

2, and moderate dilatation of the right ventricle in 4. Definite pathological changes indicative of myocarditis were demonstrable in 2 cases. One of these 2 patients on the day before death showed high T waves in leads $V_{2,3}$ and sinus arrest with nodal escape in the electrocardiogram, and a serum potassium level of 6.24 mEq./L. The pertinent histological changes of the myocardium in this case were reported as follows: "In one section there are many polymorphonuclear cells, especially eosinophils, and round cells between the muscle fibers and in the perivascular regions. Slight perivascular infiltration is to be noted in other sections. In another section there is a small subendocardial focal collection of polymorphonuclear and round cells, and the muscle detail is less distinct than elsewhere." Similar histological changes of the myocardium were found in the other case, but no electrocardiogram was obtained.

Summary. Of the 150 cases of acute poliomyelitis studied, 116 showed abnormal electrocardiograms at some time during their disease. The most common findings were, in order of frequency, abnormal T waves, tachycardia, and abnormal QT_c. Various arrhythmias, prolonged P-R interval, low voltage QRS complex, and RS-T segment changes appeared transiently and were much less frequent. Abnormal T waves usually occurred early, and prolonged QT_c persisted for the longest duration.

The incidence of abnormal electrocardiographic changes was higher in adults than in children, and in patients with bulbar or high cervical paralysis than in those with other types of lesions. It seems that no significant correlation could be demonstrated between the electrocardiographic abnormalities and the duration of fever or severity of paralysis.

Potassium studies on 81 patients were normal in 70 instances. Of those with serum potassium levels over 6 mEq./L. only 2 had high, peaked T waves in the precordial leads $V_{1,3}$.

Histological examination showed evidence of myocarditis in 2 of the 8 fatal cases. Pulmonary complications and dilatation of the right ventricle were present in more than half of the autopsied cases. The high incidence of pulmonary edema in the fatal cases of acute poliomyelitis was also reported.

Although the incidence of electrocardiographic abnormalities during the course of acute poliomyelitis is high, all the changes are considered to be nonspecific. Whereas in the majority of the patients the abnormal changes appeared and reverted to normal within the first 4 weeks, a small number of patients still showed abnormalities several months after the onset of disease.

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THE SPERANSKII METHOD OF SPINAL PUMPING IN THE TREATMENT OF ARTHRITIS*

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It is because of the stimulus provided by Dr. Wm. W. Jackson of Hot Springs, Arkansas, that the present study was undertaken. When we first became aware of his work, Dr. Jackson had already treated 80 cases by the spinal pumping method of Speranskii. Recognizing the extreme difficulty of achieving objective evaluation he was loathe to make any hard and fast claims for the method. He had, however, come to regard it as a useful tool in his armamentarium for the management of arthritis. By freely imparting his experiences, and by permitting observation of his technique and results, Dr. Jackson engaged our interest to the extent that we decided to make a trial of the method‡.

Speranskii's work[12] was originally published in the Russian language. In 1946, Gillman and Gillman[4] reported on the use, in Johannesburg, South Africa, of his spinal pumping method in the treatment of rheumatic fever and rheumatoid arthritis. These authors had previously studied and reviewed the work of Speranskii. They were stimulated to undertake a trial of the method because Speranskii's emphasis of the role of the central nervous system in disease bespoke their own interest and because they felt there was some evidence that chronic fibrosis is not necessarily an irreversible state.

Seventy patients were treated, most of them in the class of subacute and chronic arthritis. The authors considered their results roughly equivalent to Speranskii's, and of sufficient promise to warrant publication in the hope that it would provide stimulus for more extensive, systematic study.

Twelve of the 70 cases were classed as acute. In treating the data, the authors made no clear distinction between rheumatic fever and rheumatoid arthritis, designating the 12 acute cases as rheumatic fever at one point in their article and simply as acute ar-

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† Died August 11, 1951.

‡ To the best of the writers' knowledge, Dr. Jackson was the first in the United States to use the spinal pumping method in the treatment of arthritis, having begun its use on May 1, 1948. At the present time he has treated over 300 cases. Dr. Clyde Landis, Orthopedic Surgeon at the Illinois Central Hospital, Chicago, was also one of the first to use the method, and in a recent personal communication he states that his cases now number over 300. He states that his assessment at the present time is similar to that of Dr. Jackson's, namely, that the method is useful but that further investigation and study will be necessary to permit final conclusions.

thritis at another. Though only cases that had failed to respond to more conventional forms of therapy were treated, dramatic and prompt improvement was noted in a substantial number. Ten of the 12 acute cases were considered recovered by objective and subjective criteria. Twelve of the 22 chronic cases showed improvement by objective criteria, and the majority of them were relieved of pain or of the discomfort of cold extremities. The degree of benefit experienced by the subacute cases was intermediate to that of the chronic and acute.

The Gillmans felt that the method, by its effect on the central nervous system, excited a marked vascular reaction which in turn produced the beneficial result. Boucek and Lowman[2], in 1948, using spinal pumping separately and in conjunction with typhoid vaccine and auto-hemotherapy as a "vascular approach" in the treatment of rheumatoid arthritis, felt that the combination of the methods produced results which were superior to those obtained by any method used singly. They treated only chronic cases that had resisted other forms of therapy, and stated: "Of the 14 rheumatoid arthritis patients treated with a combination of Speranskii spinal pumping and typhoid vaccine-auto-hemotherapy only 1 patient remained unimproved." The primary effect from the spinal pumping was stated to be "in alleviating peripheral fibrositic and vasospastic symptoms."

Another study is that of Alimurung[1]. His is a preliminary report on 10 cases, 6 of rheumatoid arthritis, 1 of gonococcal arthritis in which the infectious phase had been controlled by chemotherapy but with disabling swelling and pain in a knee joint, and 3 of rheumatic fever. Results were reported to be good in all the cases. Temperature dropped by crisis in febrile patients, pain disappeared in 48 hours, and swelling subsided completely "except in chronic cases." Their series is a small one, but probably represents the most acute of any of the 3 studies cited above. It is also the only series in which patients were treated by spinal pumping without first having been proved refractory to extensive trials of more conventional forms of therapy. It is interesting to note that the one case of gonococcal arthritis responded, whereas 3 similar cases included in the Gillman and Gillman series failed to respond.

The only additional published report is that of Savage[11]. He observed 4 cases of rheumatoid arthritis for 1 year following spinal pumping. These were chronic cases which "had failed to respond to more rational methods." The authors recognize that the series is too small to enable them to come to any conclusions, though the case histories show that 3 of the 4 patients showed fairly prompt improvement following treatment. The fourth patient showed no improvement immediately following pumping, but "continued to have gold as an outpatient and steadily improved." At the end of the year this patient and 2 of the others were in a good state of remission. The fourth patient had relapsed and refused to have further pumping treatment. In summarizing the author states: "We saw no sign of dramatic improvement such as a return of the blood sedimentation rate to normal in 2 weeks as recorded by the Gillmans in their 12 cases of chronic arthritis. All our patients described the same type of reaction as that noted by the Gillmans—that is, a subjective feeling of heat coming on a few hours after the operation and lasting up to 48 hours. In 3 it was most pronounced at the periphery. We were, however, unable to observe any objective sign of this, such

as a rise in skin temperature or peripheral or orbital dilation of vessels."

The present report of a trial of the Speranskii method must also be considered as preliminary. It was undertaken for the sake of testing the efficacy of the method, and in the hope of finding a clue to the mechanism whereby relief, if any, was brought about. The series of cases, since they were drawn from the general practice of one of the authors, is quite heterogeneous from the point of view of type of arthritis and chronicity of the disease. We will anticipate one of our conclusions by stating that this study does not fulfill the desideratum set forth by the Gillmans, namely, that a systematic study with larger numbers of cases and adequate controls be carried out. Such a study will very probably require the facilities of an arthritis clinic. We feel that any value this report may have will not derive from any conclusions as to the efficacy of the method, but rather in any suggestion it may offer regarding the desirability of further study.

Methods. DIAGNOSIS AND EVALUATION. No special diagnostic techniques were employed. A large proportion of the patients were referred with the diagnosis already well-established. Several cases in which there was doubt and several which were considered as probable mixed arthritides have been omitted in the tabulation of results.

Evaluation was attempted primarily by careful histoy and by observation of the patient prior to treatment, and by frequent post-treatment visits for observation. Whenever possible, we tried to see the patient at least twice during the first month, once during each of the following 2 months, and at intervals of 2 to 3 months thereafter. The number of visits actually made following treatment of the 42 patients included in Table 1 totaled 267 in the 456 months of observation; average, 0.6 visit per month per patient.

In taking the history a standard list of questions concerning a variety of specific performances (ability to walk, run, bend, button clothing, drive a car, and others) was used. The replies to questions which were pertinent for each case were recorded, and the patient was questioned on these same points on successive visits. Whenever it was feasible, the patient was asked to demonstrate the performances before and after treatment.

As indicated in the section on results, several modes of more objective evaluation were attempted at one or another stage of the study. The methods were discontinued when it became evident that sufficient data had been obtained or that the method was unsuited to detection of changes.

TREATMENT. The technique described by the Gillmans was followed in its essential respects. This consisted in the withdrawal and reinjection of 10 cc. of spinal fluid through a lumbar puncture needle. The cycle of aspiration and reinjection was repeated 20 times at a slow rate (45 seconds or more for each phase). At the end of the procedure 10 cc. were removed. Most patients were treated while they were in the sitting position, since this seemed to be most easily tolerated. Rubber tubing and adapters were used to connect the syringe to the needle, because it was found to be extremely difficult to avoid displacement of the needle when the syringe was inserted directly into its hub. In many cases, a second puncture was made; tubing and adapters were used to connect this to a manometer suspended from an intravenous standard. By this means it was possible to make continuous observation of pressure dynamics.*

* These observations on pressure are not reported in the section on results, because it was not possible to make any correlations with the effects of the treatment. The Gillmans reported that they frequently found the pressure to be higher at the end of treatment than at the beginning. We sometimes found a steady rise, sometimes a steady fall, and at other times a tendency for the pressure to increase initially and then to decrease. It has occurred to us that the use of tubing to make connections may have been an undesirable modification since as much as 10 cc. of fluid were required to fill it. Effectiveness of the treatment might depend on increasing "flow" of cerebrospinal fluid by first promoting its production on reducing pressure, and then by promoting absorption on reintroduction. If such absorption–production activity were an important feature of the pumping method, we would of course have interfered with the absorption phase of it by initially depleting the patient's system in order to fill the tubing and manometer.

TABLE 1.—CLINICAL DATA ON 42 PATIENTS WITH VARIOUS TYPES OF ARTHRITIS TREATED WITH SPINAL PUMPING

Patient	*Age*	*Sex*	*Yrs. of Illness*	*Months since Therapy*	*Stage of Rheumatoid Progression*	*Functional Capacity Before*	*Functional Capacity After*	*Grade of Response to Therapy*	*Improvement in Sleep*
RHEUMATOID ARTHRITIS									
1	52	F	20	22	IV	IV	III	II	I
2	47	F	20	15	IV	IV	IV	IV	III
3	44	M	3	6	II	II	II	IV	II
4	43	M	10	18	IV	III	I	I	I
5	45	F	6	17	II	II	I	II	–
6	51	F	27	15	IV	II	II	IV	III
7	44	F	3	14	IV	III	I	II	I
8	64	F	28	14	IV	II	II	III	–
9	53	F	3	13	II	III	II	III	I
10	55	F	23	13	IV	IV	IV	IV	III
11	57	F	3	6	II	III	III	IV	III
12	50	F	2	13	II	III	III	III	–
13	57	F	12	12	III	IV	III	II	I
14	45	F	4	12	II	III	III	IV	III
15	53	F	11	11	IV	IV	IV	IV	III
16	45	F	12	10	I	II	II	II	II
17	50	M	7	12	I	II	II	III	–
18	58	M	17	11	IV	III	III	IV	III
19	65	F	4	12	II	II	II	III	II
20	57	F	5	10	III	III	III	III	–
21	54	F	20	8	II	III	III	IV	–
22	47	F	23	8	IV	II	II	IV	II
23	39	F	5	7	II	II	II	IV	III
24	44	F	4	6	II	II	II	III	II
25	50	F	1	1	II	II	II	IV	III
26	52	F	10	3	II	III	III	III	II
Average	53		11	11					
ANKYLOSING SPONDYLITIS									
27	32	M	5	17		II	I	II	I
28	37	M	33	14		II	II	III	I
29	43	M	15	10		IV	IV	IV	–
30	38	M	10	4		II	I	III	–
31	36	M	12	3		II	II	IV	III
Average	37		15	10					
OSTEOARTHRITIS									
32	61	M	2	18		III	I	II	I
33	61	F	10	15		II	I	II	–
34	53	M	8	13		II	I	I	I
35	52	F	15	13		III	I	I	I
36	49	M	27	12		II	II	III	III
37	29	M	6	12		II	I	III	II
38	67	F	10	11		II	II	IV	III
39	51	M	4	10		III	I	I	I
40	52	F	4	7		II	I	II	I
41	63	F	16	6		III	II	III	–
42	57	M	10	2		III	II	II	–
Average	59		11	12					

The only additional modifications of the method described by the Gillmans were 1) deliberately to slow the rate of pumping to as slow as 5 minutes per cycle of aspiration and reinjection, and 2) to prolong the period of salicylate administration. (The prescribed method was to administer 10 gm. daily during the 24 hours preceeding teatment and for 24 to 48 hours following. When we prolonged medication beyond the 72-hour period the dosage was reduced.)

Results. The results have been summarized in Table 1. In preparing this

TABLE 1.—SUMMARY OF THE RESULTS OF SPINAL PUMPING ON 26 CASES OF RHEUMATOID ARTHRITIS, 5 OF ANKYLOSING SPONDYLITIS, AND 11 OF OSTEOARTHRITIS

Except for the column headed, "Improvement in sleep," all the columns employing Roman numerals are based on the criteria established by Steinbrocker *et al.*[13]. The criteria used in making the evaluations are as follows:

STAGE OF RHEUMATOID PROGRESSION

I. Roentgenologic signs absent or limited to osteoporosis; no muscular atrophy, extra-articular lesions, joint deformity, or ankylosis.

II. Roentgenologic changes not advanced beyond slight subchondral bone destruction; slight muscular atrophy; extra-articular lesions may be present; no joint deformity or ankylosis.

III. Osteoporosis, cartilage and bone destruction; muscular atrophy extensive; extra-articular lesions may be present; subluxation, ulnar deviation, and/or hyperextension; no ankylosis.

IV. The same as III except that ankylosis must be present.

FUNCTIONAL CAPACITY

I. Complete: Able to carry on all usual duties without handicaps.

II. Adequate for normal activities, despite handicap of discomfort or limited motion at one or more joints.

III. Limited: Only to a few or none of duties of usual occupation or self care.

IV. Incapacitated, largely or wholly: Bedridden or confined to wheelchair; little or no self care.

GRADE OF RESPONSE TO THERAPY

I. Complete remission.

II. Major improvement.

III. Minor improvement.

IV. Unimproved.

In the rheumatoid arthritis cases the estimate of improvement is based on 7 signs of rheumatoid activity as outlined by Steinbrocker, *et al.* As explained in the body of the text, the degree of response in the ankylosing spondylitis and osteoarthritis cases was estimated differently.

IMPROVEMENT IN SLEEP

—No impairment in sleeping ability prior to treatment.

I. Marked improvement: Awoke frequently during the night prior to treatment; sleeps soundly and uninterruptedly following treatment; feels refreshed on awakening in the morning.

II. Moderate improvement: Includes patients whose sleep was not too severely impaired prior to treatment and who recovered fully following treatment, and patients with severe sleep disturbance who still did not sleep entirely without interruption following treatment.

III. No improvement: Patient did not feel his sleep was improved following treatment.

table we have used the criteria as established by Steinbrocker, Traeger, and Batterman[13] to classify the rheumatoid arthritis patients as to stage of rheumatoid progression, functional capacity, and grade of response to treatment. The data considered desirable by these authors in making the classification were not completely available in each case, but the number of criteria they present is sufficiently broad to have enabled us to make the greater majority of judgments with a high degree of confidence.

The patients with ankylosing spondylitis and osteoarthritis have been included in Table 1. It is recognized that the criteria established by Steinbrocker *et al.* are intended to apply only to rheumatoid arthritis, and hence we have not completed all of the columns for the table. Functional capacity has

been estimated by the same criteria in all 3 forms of arthropathy, whereas degree of response to therapy, though indicated by the same symbols in all 3 varieties of disease, was based primarily on history and functional capacity in the ankylosing spondylitis and osteoarthritis cases.

One criterion of improvement which the authors felt to be of value in estimating response to therapy in the patients was that of improvement in sleep. An important complaint of many patients with rheumatic disease is that sleep is frequently interrupted, and it seems likely that the patient's estimate of the degree of soundness of his night's sleep is less likely to be distorted by factors of suggestion than are many other indices of possible improvement. All patients were systematically questioned on this subject prior to treatment and in subsequent interviews. For the convenience of the reader, the meaning of the symbols used in Table 1 is given on the facing page.

The results make a statistically poor showing in rheumatoid patients. Those exhibiting remission or major improvement totaled less than 25%. One might be inclined to credit the treatment with greater efficacy than this figure indicates on considering that the majority of the cases were chronic (50% with a duration of 10 or more years) and in an advanced stage of rheumatoid progression, except for the fact that improvement was as often seen in the chronic advanced cases as in the more acute, less advanced ones.

If improvement in sleep may be regarded as a measure, the efficacy of the treatment is somewhat increased. Of the 20 individuals complaining of difficulty in sleeping prior to treatment, half attested a degree of improvement which was graded as moderate or marked. It is probably also of significance that there were additional patients who experienced transient improvement in sleep. In going over the records, the authors would have assigned at least 11 of the cases to a higher grade in the category of RESPONSE TO THERAPY if the time of maximum improvement had been used for making the evaluation. The period of duration of gains, which were subsequently lost, ranged from a few days to a few months. These transitory gains were not considered in preparing the table.

In the ankylosing spondylitis cases there is again an unimpressive statistical record. Only 1 of the 5 is graded as having shown major improvement. In spite of this, the authors regard the treatment as having been worth while in 4 of the 5. The value lay in 1 instance in persistent amelioration of intolerable pain and, in another, graded as showing minor improvement, in transitory changes which were of such a pronounced degree as to have been totally unexpected. To be more explicit, these transitory changes occurred in one case in which the authors, though advising the patient of their willingness to administer the treatment, advised him also that they could not expect it to be of any benefit in his case. The patient, age 37, had suffered arthritis for 33 years. He exhibited a very marked kyphosis of the dorsal and lumbar spine with Roentgen-ray evidence of ankylosis throughout the same region. He had been unable to lie in the prone or supine position for 14 years, and was therefore astonished to awaken and find himself prone on the morning following treatment and in this or the supine position on a number of later occasions.

The method of spinal pumping proved to be unexpectedly efficacious in the osteoarthritides. Of the 11 pa-

tients who were treated, only 1 is graded as unimproved and all but 3 of the others showed improvement rated as better than minor.

Table 2 presents the available data on sedimentation rates. It is apparent at a glance that the treatment did not produce any significant alterations.

Range of motion studies were carried out on 15 subjects. Significant changes occurred in only 2 cases. It is interesting to note that others of the 15 patients demonstrated improved functional capacity despite lack of demonstrable increase in range of joint motion. This is easily understandable, since decrease in pain alone, or improvement in motion which is less than the range of error of measurement, may permit the performance of acts which were formerly impossible. Though consistent improvement in

TABLE 2.—SEDIMENTATION RATES IN ARTHRITIC PATIENTS TREATED WITH SPINAL PUMPING

Patient	*Before*	*1 wk.*	*2 wks.*	*3 wks.*	*4 wks.*	*2 mos.*	*3 mos.*
RHEUMATOID ARTHRITIS							
1	27						
2	82	75					
3	58	54					
4	26						
5	13	6				10	
6	27	23	15			24	
7	25	16	8			15	7
8	10						33
9	85		28				
10	50	46		47	54	45	
11	60	61	59		70		78
12	19	19	19				
13	104						
14	40	48	51				
15	69	67	52		76		
16	43	50					
17	22					31	
18	84	76	75	84		92	
19	59	36	53	60			
20	56	51	60	49			
21	53	63	53			48	110
22	34	18	23				
23	75	73		60			
24	40	20		32		35	
25	3	12					
26	80	70		65		77	74
ANKYLOSING SPONDYLITIS							
27	14					6	
28	55	32			57		53
29	36	50		33		65	49
30							
31	30	50	60				
OSTEOARTHRITIS							
32	36	35					
33	22	16	10				34
34	5						
35	11		17		12	9	14
36	6			3			5
37	16	30	36	20	29		
38	8	13	14	10		6	9
39	35	18	41				
40	20	17		20			
41	60	40		24		104	
42	11	8			5		

range of motion as determined by objective methods would have been a welcome finding, this criterion is a rigorous one and failure to meet it still allows considerable latitude for improvement in the patient's condition.

It is perhaps important to note that no persistent ill effects were observed to result from any of the treatments. Six of the patients experienced nausea for periods ranging from 1 to 10 days; 12 suffered lumbar puncture headaches which lasted for periods ranging from a few hours to 7 days. The occurrence of nausea, headache, and such reactions as sweating, change in body temperature, and flushing were observed in an attempt to correlate them with therapeutic benefits. Though reactions such as these did occur, the authors were unable to detect any evidence that they correlated with the results.

The following 4 case histories have been chosen for presentation, not because they are representative of the series, but rather because the changes subsequent to spinal pumping took place so promptly and were of such a nature as to make it difficult to understand how they could have occurred spontaneously or as the result of suggestion.

Case Reports. CASE No. 1. Patient No. 1: Rheumatoid Arthritis; white female, age 52; housewife.

The patient had been a wheel-chair invalid for 4 years, and was experiencing severe generalized pain and aching. She was unable to shift her position in the wheel chair without help because of the spasms of pain induced by voluntary effort. Slight jostling was dreaded because of similar effects; the patient, for example, was unable to tolerate having her grandchildren on her lap. She was unable to lie in one position for more than 30 to 60 minutes at night, and then required assistance to turn from side to side; the supine position could not be tolerated. Soft tissue swelling was pronounced in the distal portion of all the extremities. The fingers showed moderate ulnar deviation and flexion deformity. Roentgen-ray changes were pronounced, with an appearance of complete bony ankylosis in the right hip. Destructive changes with contracture were present at the shoulder, elbow, hip, and knee joints.

During the 19 years since the onset of the disease the patient had had the usual variety of treatments, including physiotherapy, various forms of foreign protein therapy, nicotinic acid, and Roentgen therapy. Some of the earlier treatments, especially intravenous typhoid, produced undesirable results, whereas temporary relief had been obtained at times with physiotherapeutic measures. Wheel-chair invalidism followed a period of several months of bed rest enforced because of an episode of hematemesis of unknown cause.

Laboratory data were not available prior to treatment.

Treatment was carried out in the lateral decubitus position and required 63 minutes. The full course of 20 aspirations and reinjections was completed, though not without considerable difficulty in maintaining open communication through the lumbar puncture needle. The patient experienced some headache, marked ringing and deafness, and mental cloudiness during the treatment. An hour after the conclusion of the spinal pumping the patient reported that she felt "as though things let loose and all her joints sagged down closer to the bed". Three hours later she felt perfectly comfortable even though she had been lying quietly on her back all afternoon in a position which would have been intolerable for even a short period of time before treatment. At this time also the patient had gained some motion in her right hip, could extend her left arm over the top of the head for the first time in years, and found that passive spreading of the fingers of the right hand, formerly very painful, caused no discomfort.

Violent nausea developed and was present for the first 5 days. It then cleared completely and the patient was essentially free of pain except for an area of tenderness in the right hip. She soon learned to jerk herself to a sitting position in bed, to roll over unassisted, to raise her feet from the floor to the edge of the bed, and to perform various tasks of self-help more efficiently. She slept well, and her eagerness to arise contrasted with her previous morning lethargy and longing for "just another hour of sleep" before arising.

Just prior to treatment roentgenograms of the right hip were made. Fig. 1 shows an antero-posterior view with the limb in its

greatest possible degree of abduction, and casual inspection of the film suggests that the limitation of motion was due to destructive and fibrotic changes. That the limitation was not due to ankylosis is clear from the film taken one day after the treatment, showing an unexpected degree of abduction, which was accomplished with relatively little pain.

Another unexpected sequel to the treatment was an apparent change in the degree of refractive error of the eyes. The first observation on this was after recovery from post-treatment nausea, when the patient reported that accumulated mail had been read without realizing until later that she had not been wearing glasses. This was something which had been impossible before spinal pumping. Two weeks later she demonstrated ability to thread a needle easily without the use of glasses, when before she not infrequently found herself trying to thread the tip rather than the eye of the needle, even with the aid of glasses. The change in vision gradually reverted to the pre-treatment status.

Improvement continues to the present date, though there has been some regression from the state of maximum benefit, which was seen 5 to 6 months after treatment. At that time the patient made frequent trips to a bathing beach, learned to walk unassisted in the water, and to take a few steps on land with some assistance from her husband.

CASE No. 2. Patient No. 7: Rheumatoid Arthritis; white female, age 44; housewife.

When first seen on September 23, 1949, the patient was experiencing pain and aching in the entire right upper extremity, in the right hip, in both knees and feet. The third and fifth digits of the right hand showed typical fusiform swelling with some ulnar deviation and flexion deformity. Soft tissue swelling and tenderness were present in both knees. Sleep was severely disturbed: the patient was unable to lie on her right side for more that 30 minutes without being awakened by pain.

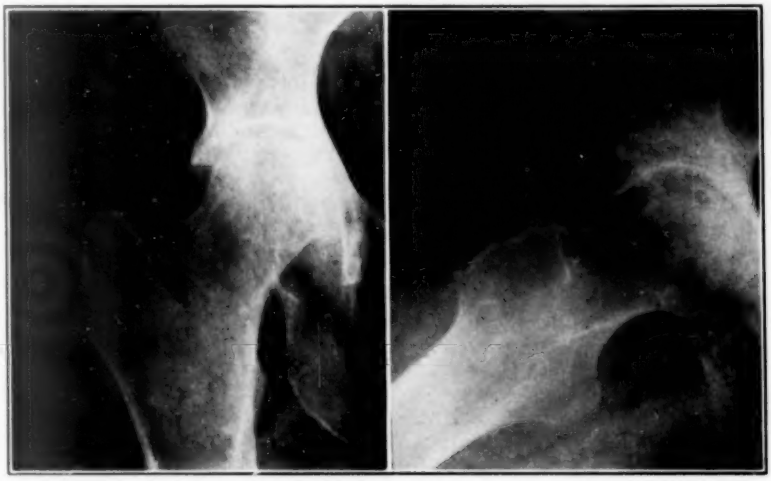

FIG. 1.—Roentgenograms of the right hip of Patient 1. Left, view was taken the day before treatment with the limb in the greatest possible degree of passive abduction. Right, a similar view taken on the day following treatment, the markedly increased degree of abduction having been accomplished with relatively little pain. The figures are published because of the circumstance that the roentgenologist and others who studied the films felt that the extent of pathological change in the hip joint would not permit greater abduction than that which was seen before treatment.

Some activities, such as shopping, driving a car, and manipulation of a vacuum cleaner had been given up entirely. She was slow and awkward in the performance of other tasks, such as making beds, and a special stool had been adopted for use in the kitchen because of difficulty in arising from a chair of ordinary height.

At the onset of the disease, 3 years prior to the time the patient was first seen by us, the

condition was diagnosed as gout and purine diet prescribed. A year later rheumatoid arthritis was diagnosed at a state hospital and paraffin baths were recommended for the hands and feet. There had been no other treatment except for the use of mild analgesics. History indicated that the temporomandibular joint as well as most of the joints of the extremities had been involved at one time or another.

Laboratory data included: sedimentation rate (Westergren), 25 mm.; erythrocytes 3,870,000.

Treatment was conducted with the patient in the sitting position. The actual period of manipulation lasted 1 hour and 42 minutes, the operator attempting to maintain an even rhythm of 5 minutes for each cycle of aspiration and reinjection of 10 cc. of spinal fluid. Some drowsiness, sweating, and "quivering" occurred during the treatment, but it was otherwise without incident. Cerebrospinal fluid pressure fell slowly and steadily during the procedure, being 6 to 7 cm. lower at the conclusion than at the beginning.

The patient remained in bed for 2 days, experiencing neither headache nor nausea. She felt well the day following treatment, and believed there was some improvement in motion of the knees. By the second day motion of her hands and toes was freer, and tenderness which had been present at the base of the proximal phalanges had disappeared.

By the 12th post-treatment day the patient had scrubbed the floor on hands and knees, driven the car for the first time in 2 years, discarded the special kitchen stool, and and found greater ease in performance of many tasks of self-help. She was seen at intervals of 1 to 2 months and continued to get along well. Eight months following treatment she was "able to do anything," and demonstrated her ability to *run* up a steep and stony hillside. Sleep had been characteristically sound and undisturbed since treatment. At the end of the period of observation included in the study (14 months) the patient still regarded herself as essentially recovered. There had been some swelling of the fingers and occasional transient aches, but household and social activities were carried on without handicap.

Case No. 3. Patient No. 27: Ankylosing Spondylitis; white male, age 32; student.

When first seen, the patient was under the care of an ophthalmologist for iritis of the right eye. Arthritic complaints concerned the lower back and hips. There was stiffness and aching. It was impossible to bend forward sufficiently to bring the fingertips to the knees. Sleep was markedly disturbed by spasms of the gastrocnemius muscles as well as by aching and pain in the spine and hips. The patient was in the habit of using pillows to prop himself into the most comfortable position and found it necessary to readjust his position frequently during the night.

Past history revealed that the patient developed "terrific backache" while active in the tank corps in 1945 in Japan. A diagnosis of ankylosing spondylitis was not made until several years later, but the patient was discharged from the Army with this diagnosis and a disability pension. Aching, which had at first been present in the morning only, was stated to have been present constantly for an 18-month period prior to treatment. Roentgenogram showed sclerosing of the facets of the lumbar vertebrae and of the sacro-iliac joints.

Laboratory data included: sedimentation rate (Westergren), 14 mm.; red cells, 4,630,000; hemoglobin, 95%.

The sitting position was adopted for the treatment, which required 1 hour and 12 minutes. The operator attempted to maintain an even rhythm of 3½ minutes per cycle of aspiration and reinjection. Except for pronounced warmth and perspiration, no unusual effects were noted. During the latter half of the treatment, the patient stated that he must be dreaming, but his eye seemed to feel better and he was able to peer out from under the bandage without experiencing discomfort from the light.

The morning following treatment a consultant pronounced the iritis cleared; conjunctivitis persisted for another week. Within 24 hours following treatment the patient was able to put on his own shoes, something which he had been unable to do for several months. While in the hospital he slept well at night and dozed a good deal during the day.

The patient remained essentially free of symptoms for the next 6 months. He sought and found employment, he slept well regularly without the aid of props or sedatives, and engaged in fairly strenuous physical activity. During the first 80 days following treatment there was a 30-pound weight gain.

During the 7th to the 17th months the patient had minor arthritic aches, but continued working except for an interval of several weeks when a temporary iritis developed in the left eye.

Case No 4. Patient No. 32: Osteoarthritis; white male, age 61; contractor.

This patient was referred because of severe pain in his left hip. He walked with a pronounced limp, felt the pain constantly, was unable to raise the left foot higher than the right ankle, and slept very poorly. He was in the habit of getting up at 2 to 3 a. m. and sitting in a chair for a time because of inability to sleep in spite of the use of "strong sleeping capsules." He had not attempted to work for the 6 months preceeding treatment.

The hip had begun to cause significant discomfort 18 months earlier. Various forms of medical therapy had been unavailing. Roentgenography revealed what appeared to be bony ankylosis. The orthopedic surgeon who referred the patient suggested a trial of the spinal fluid treatment, recommending surgery for implanation of a vitallium cup if that failed.

Laboratory data included: sedimentation rate (Westergren), 36 mm.; red cells, 4,730,000; hemoglobin, 95%.

Treatment was initiated with the patient in lateral decubitus, but he was very shortly shifted to the sitting position because of intolerable pain. Total pumping time was 63 minutes, the operator attempting to maintain an even rhythm of 3 minutes per cycle. Cerebrospinal fluid pressure dropped 7 to 8 cm. below the initial level by the end of treatment. No untoward subjective effects occurred.

The patient slept 12 hours the night following treatment, and was able to rest comfortably on his side the next morning. This position had not been comfortable for many months. On the second day there was essentially no pain in the hip and only a slight limp. The left foot could be raised to the level of the knee.

At 10 days the patient returned to work, and has remained on the job during the ensuing 18 months. He worked 10 hours a day regularly the following summer, often at such jobs as leveling concrete. The patient has slept well every night since treatment, without exception and without sedatives. There have been some recurrence of pain and some increase in limping during recent months. This has not been sufficient to interfere with his work or sleep, but to make him consider, albeit reluctantly, the possibility of another pumping treatment with the aim of preventing further regression. The patient states that he would not consider further treatment at this time if he could be certain that no further regression would occur.

Discussion. Experience with the Speranskii method of spinal pumping has served to increase, rather than decrease, our interest in the procedure. We find it difficult to assess the basis of our own attitude, to say nothing of the difficulty of attempting to transmit it to the reader. We are undoubtedly influenced in part by the realization that satisfactory answers to problems of etiology and treatment of arthritis are still wanting. The need which exists warrants vigorous efforts to trace out any clues which hold promise of contributing to eventual resolution of the problems. (This statement is made with full realization of the dramatic importance of recent discoveries of the role of endocrine factors. These discoveries, casting an entirely new light on the basic nature of arthritic and other disease processes, provide increased incentive to make explorations along unorthodox lines.)

Our continued interest in spinal pumping is not, however, based primarily on the philosophy of grasping at straws. Whereas we must insist that the Speranskii method as it has been practiced by us* is not the final solution to the problem of treatment of rheumatoid arthritis, we have a strong conviction that it touches on an important aspect of the disease. The *total* impression gained by observing those patients who do respond is that they have been directly affected by the treatment. Certain intangibles, which

* The results reported in this study are based entirely on cases receiving a single treatment. In a personal communication, Dr. Wm. Jackson reports that it has not been unusual in his experience for patients to fail to show benefit after 1 and even 2 treatments, and then to respond satisfactorily with further pumping therapy. Instances in which second and third treatment apparently proved to be beneficial were also quoted in the literature which has already been cited.

are not amenable to statistical treatment or to adequate presentation via the case history method, contribute to this impression. These intangibles include such things as apparent sense of well-being, promptness of response, evaluation of results by patients who have submitted to many previous forms of treatment, the assumption of unaccustomed postures during sleep, the effect on sleep itself, and the like. These effects might also be interpreted as supporting the argument that the results were due to a potent form of psychotherapy. The authors see no easy means of resolving the problem on the basis of available data. In reality, they can do little more at present than to urge their conviction that further work is needed, and to outline what appear to be important realms for further investigation.

Some of the questions which have been raised are amenable to study by laboratory experimentation, and it is perhaps in this realm that further work is most urgently needed. If cerebrospinal fluid manipulation does have a significant effect on the pain of arthritis, it at once suggests that the increase in pain which is experienced by many patients when the barometer drops may be due to the relationship between atmospheric pressure and cerebrospinal fluid pressure. Thorner[15] has shown that variations in atmospheric pressure cause prompt adjustments in arterial and cerebrospinal fluid pressures in normal subjects. This suggests one important field for experimental study.

The method of forced drainage as practiced by Retan[8-10] and Kubie[5] and others in the period around 1930 should be reviewed in connection with results reported for the method of spinal fluid pumping. It is extremely suggestive that good results were obtained in acute chorea by the method of forced drainage* and that literature on spinal pumping points to rheumatic fever as the condition which has responded most dramatically.† The suggestion that acute rheumatic disease has responded to 2 quite different modes of cerebrospinal fluid manipulation raises the question as to whether or not the "forcing" aspect of the one method and the "pumping" aspect of the other may not be 2 means of accomplishing the same result.

* Reese and Shulak[7] state: "Retan was able to influence the signs and symptoms in many cases, to improve acute virus infections and to *cure 14 cases of acute chorea*" (*Italics are the authors'.*)

† As stated in the introduction to this paper, the Gillmans achieved their best results in the 12 cases which they at one point designated as rheumatic fever and at another simply as acute arthritis. Savage[11], in comparing results on his 4 cases of rheumatoid arthritis with the results of the Gillmans, is presumably referring to these 12 cases when he states: "We saw no sign of dramatic improvement such as a return of the sedimentation rate to normal in 2 weeks as recorded by the Gillmans in their 12 cases of chronic arthritis." It is conceivable that results are being compared on 2 different disease entities.

The present authors know of only one series of rheumatic fever patients treated by the Speranskii method in the United States. In personal communication, Dr. H. William Elghammer, Department of Pediatrics, Loyola University, Chicago, states that he has treated 6 children with rheumatic fever and polyarthritis, 5 of which responded similarly to those reported by the Gillmans. In 3 cases of rheumatoid arthritis definite improvement resulted in only 1 case.

If it is assumed that the Gillmans' 12 acute cases were rheumatic fever and the others were rheumatoid arthritis, then it appears that the reported percentage of improvement in rheumatoid arthritis is roughly equal to that of the present study, whereas a much higher "cure rate" could be expected in rheumatic fever.

The experiences of the present study have not provided any obvious clues as to the possible mechanism by which spinal pumping may have a beneficial effect. Reference has already been made to the possibility that there might be an influence on "circulation" of the cerebrospinal fluid. Sullivan[14], Mortensen[6], Faber[3] and others have shown that materials of certain kinds introduced into the subarachnoid space will appear in other tissue spaces of the body in astonishingly short periods of time, and, conversely, that materials introduced into the nasal cavity or into nerve sheaths pass readily into the subarachnoid space. Further study of the degree of interchange of fluid under normal and pathological conditions might prove rewarding, even though the precise significance of such interchange would remain to be elucidated.

The authors have speculated as to the possible relation to ACTH and cortisone effects. Mood changes which were noted, as well as some of the results illustrated by the case histories, are suggestive, but no direct evidence has been obtained. One of the more intriguing possibilities which presents itself is that the hypothalamus and the pituitary gland may be influenced by way of cerebrospinal fluid conditions.

Summary and Conclusions: 1. The effects of the Speranskii method of spinal pumping have been studied in a variety of arthritides with a view to possible elucidation of the role of cerebrospinal fluid dynamics in health and disease.

2. The observed effects, though difficult to evaluate, have served to stimulate the continued interest of the authors. Two independent workers report that they have each treated over 300 cases and believe the method to be a useful one.

3. No persistent ill effects have been observed to result from the treatment.

4. It has been suggested that more information is needed on the relation between cerebrospinal fluid pressure and atmospheric pressure. Other basic problems which should be studied concern a) the normal rate of interchange of fluids between the subarachnoid space and other tissue spaces, and b) the influence of changes in cerebrospinal fluid pressure on function of the hypothalamic nuclei.

Since the time of preparation of the manuscript, an additional 11 cases have been treated by the method described in the body of the article. It is necessary to point out that there has been one death which occurred 15 hours following completion of the treatment. Autopsy revealed evidence of a cerebellar pressure cone and a fourth ventricle which was reduced in size to a mere slit-like opening. In the absence of any gross or microscopic evidence of an expanding lesion, of hemorrhage, or of edema it is presumed that some anomaly such as an Arnold-Chiari malformation existed. Death must in this instance be attributed directly to the fact of spinal fluid manipulation, though it is probable that a simple diagnostic lumbar puncture would have produced the same result. An additional noteworthy fact about this case is that there was gross and microscopic evidence of adrenal atrophy, with absence and fragmentation of the nuclei in many areas of the zona fasciculata. This was no doubt due to earlier cortisone treatment, though the hormone therapy had been discontinued 24 weeks prior to the time of death.

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CLINICAL EXPERIENCE WITH THE ANTICOAGULANT, TROMEXAN*

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Tromexan (3, 3-carboxymethylene bis-(4, hydroxycoumarin) ethyl ester), a new anticoagulant, was originally synthesized by Rosicky of Czechoslovakia in 1944[15], and the first large scale clinical study was reported by Reinis and Kubik in 1948[12]. The early experimental and clinical investigation of the drug was carried out in Europe[2, 5,9,12,13]. Burke and Wright[4] and Solomon and his associates[15] reported studies on the preparation for the first time in the United States, followed by several other reports which have appeared in the American literature[1,7].

Since the advent of dicoumarin therapy in the treatment of thromboembolic disease, the most difficult problems arising in the management of such cases have been: 1) making reliable prothrombin determinations, and 2) combating the cumulative effects of the preparation and the resultant hemorrhagic tendencies. From an analysis of the reports appearing in the literature, it would appear that Tromexan was a safer and more rapidly excreted anticoagulant than any of the previously synthesized dicoumarin preparations[2-5,13].

The purpose of this communication was to study and evaluate a consecutive series of patients on the wards of a large municipal hospital who were candidates for anticoagulant therapy, and to record their clinical and laboratory response to the drug. The Tromexan activity was studied by repeated prothrombin determinations utilizing 2 thromboplastin preparations, Thromboplastin A† and Thromboplastin B. An attempt was made to compare the results so that a standard procedure for performing reliable prothrombin determinations could be established permanently at this hospital. Furthermore, it was desirable to evaluate the effectiveness of the water soluble Vitamin K preparations in combating the hypoprothrombinemic tendencies of Tromexan.

Materials and Methods. Fifty consecutive cases were studied in which the following lesions were present: myocardial infarcts, in 22 cases; thrombophlebitis, in 17; frostbite, in 3; cerebral thrombosis, in 5; postoperative mesenteric thrombosis, in 1; postoperative pulmonary embolism, in 1; and peripheral arterial embolism, in 1.

Prothrombin time determinations were carried out daily on each patient with whole (100%) plasma according to the 1-stage Link–Shapiro modification of the Quick method, utilizing the 2 thromboplastic substances under similar standard conditions. The blood specimens were obtained at the same time each day and the tests were performed within an hour after collection in dry double oxalated tubes. If prothrombin times were more than 45 seconds, blood was re-drawn and the test repeated. Tromexan was dispensed once

* Supplied by the Geigy Company, New York.

† Thromboplastin A is Simplastin, supplied by Chilcott Laboratories, Division of the Maltine Company, Morris Plains, New Jersey.

daily at the same time to all patients.

An attempt was made to maintain the prothrombin time arbitrarily between 28 and 45 seconds or approximately 2 to 2½ times that of the patient's control in seconds. These levels were maintained unless untoward reactions, that is, signs of bleeding or drug resistance, were encountered. During the administration of the drug all medications having a hypoprothrombinemic tendency were eliminated.

Repository Heparin (Lederle)* 20,000 units was administered on admission in 31 cases in addition to Tromexan, and serial coagulation times were determined.

Dilution curves were constructed. Serial dilutions were plotted against time in seconds of prothrombic activity, utilizing Thromboplastin A and B (Fig. 1). Freshly prepared rabbit brain substance was used as a control check†.

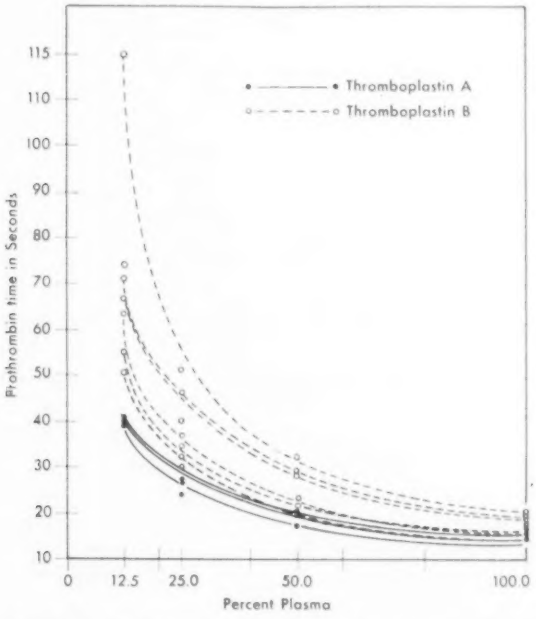

FIG. 1.—Curves in which serial plasma dilutions are plotted against prothrombin time in seconds, utilizing 2 thromboplastic substances (A and B) at various control levels. Note that these curves are made up of averages and that in certain areas curves representing the same thromboplastic substance tend to approximate each other.

Urinalysis was performed before therapy was instituted, at bi-weekly intervals, and whenever marked hypoprothrombinemia existed or there were any indications of bleeding. Special emphasis was placed on microscopic hematuria. Basal prothrombin determinations, bleeding time (Duke method), clotting time (Lee White method), complete blood count, blood typing, and Rh determinations were made before commencing treatment.

When therapy was discontinued, prothrombin time determinations were performed daily until pretreatment levels were approximated.

Results. The duration of anticoagulant therapy in this series ranged from 2 to 46 days. In most instances an initial dose of 1,500 to 1,800 mg. of Tromexan was required in order to ob-

* Supplied by Lederle Laboratories, Division of American Cyanamid Company, Pearl River, New York.

† Prepared according to the method of Quick.

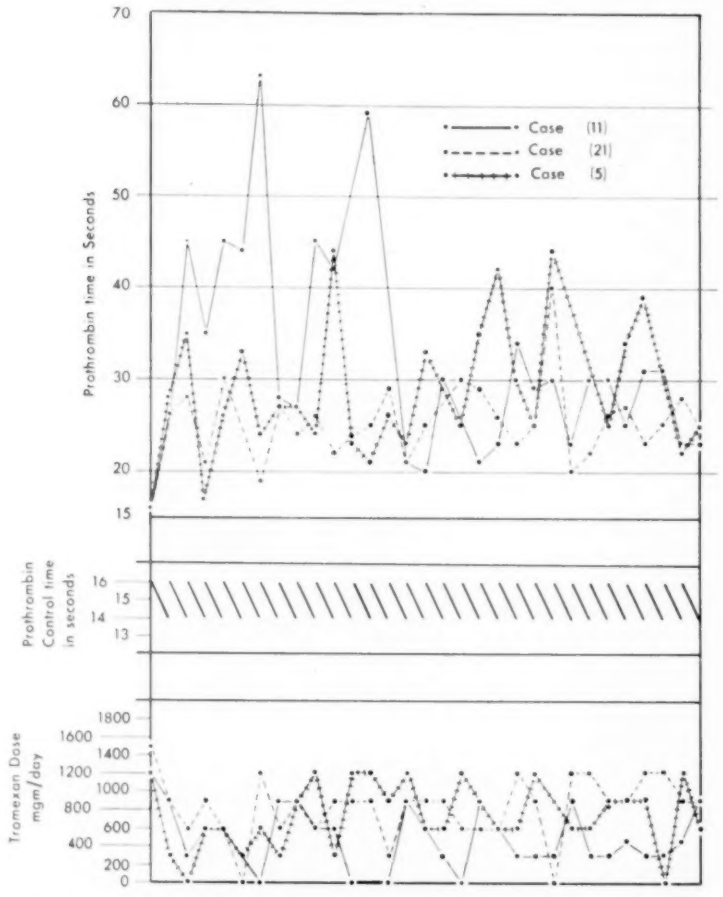

FIG. 2.—The marked daily fluctuations of prothrombin time in seconds for 3 representative patients on Tromexan therapy.

tain therapeutic prothrombin time levels in 24 hours. No correlation between size of dose and body weight could be determined. When the initial dosages ranging from 900 to 1,200 mg. were administered, an inadequate prothrombin time elevation was observed in 24 hours and additional Tromexan was required before therapeutic levels were observed at the end of 48 hours. After the first 24 hours, a second administration of Tromexan ranged between 600 and 900 mg. Occasionally 1,200 mg. were required and in certain resistant cases higher daily dosages were employed. The daily maintenance requirement after the first 48 hours was from 300 to 900 mg. In some instances only 150 mg. of Tromexan were dispensed.

Transitory cumulative effects were noted at some time during therapy in 15 cases, 13 of which had no clot formed in the prothrombin determination at various intervals. These cumulative phenomena were adequately controlled when the medication was omitted for 24 to (occasionally) 48

hours. In all cases studied, difficulty was encountered in attempting to maintain prothrombin times at a constant proposed therapeutic level. Irregular daily fluctuations were observed when curves were constructed so that daily prothrombin times were plotted against day of therapy, as evidenced graphically by irregular spikes in the resultant curves. In no instance was a level plateau type of curve observed on a single daily dose schedule of Tromexan (Fig. 2).

TABLE 1.—PROTHROMBIN TIME IN 9 PATIENTS RECEIVING WATER SOLUBLE VITAMIN K DURING THE COURSE OF TROMEXAN THERAPY

Case No.	*Initial Proth. Time (in seconds)*	*Vitamin K mgm.*	*Tromexan mgm.*	*Resultant Prothrombin Time (24 hr. in sec.)*
18 (R. S.)	37	30 i.m.*	300	21
19 (L. W.)	32		—	19
35 (M. T.)	54	80 i.m.	—	29
41 (J. S.)	31	75 i.v. 40 i.m.†	—	20
44 (S. T.)	60	72 i.v.	—	24
46 (M. K.)	42	75 i.v.	450	26
48 (H. W.)	31	72 i.v.	900	17
49 (M. T.)	31	72 i.v.	600	24
50 (S. K.)	50	75 i.v.	—	18

* i.m.: intramuscularly
† i.v.: intravenously

After discontinuing therapy the prothrombin time returned to pretreatment levels in 24 to 72 hours, with an average of 48 hours.

Nine cases were selected at random and given water soluble Vitamin K ranging from 30 to 75 mg. intramuscularly or intravenously*†. Within 24 hours the prothrombin time in seconds decreased on an average of 13.3 seconds in 4 cases receiving the estimated Tromexan for the day as well as the Vitamin K. In only 1 instance did the prothrombin time reach pretreatment levels in this series. In the 5 cases in which the drug was omitted and Vitamin K administered, the prothrombin time in seconds dropped an average of 23.4 seconds. In all cases, previous to Vitamin K administration, therapeutic or higher prothrombin times were present (see Table 1).

In a control series of 18 cases under similar conditions in which Tromexan was omitted for 24 hours, the prothrombin time decreased an average of 14.5 seconds.

The prothrombin control level for Thromboplastin A was 15 ± 1 second, and for Thromboplastin B was 17 ± 3 seconds. Thromboplastin A in all determinations gave constant control levels with little variation.

In 28 cases receiving an initial dose of both Repository Heparin and Tromexan, coagulation times 24 and 48 hours later were not increased over the calculated increase to be expected by a single dose of Heparin alone. No untoward or toxic effects were observed when both medications were administered simultaneously.

Toxic Effects. Although the number of cases in this series is too small to be significant statistically, 4 cases (8%) exhibited at some time during therapy with anticoagulants microscopic hematuria which could be directly attributed to Tromexan toxicity. No gross hema-

* Synkavite, supplied by the Hoffman LaRoche Company, Nutley, New Jersey.
† Hykinone, supplied by the Abbott Laboratories, North Chicago, Illinois.

turia was observed at any time during this study. One patient developed gastrointestinal bleeding which persisted for 24 hours. The omission of Tromexan and the administration of multiple injections of water soluble Vitamin K (30 mg. intramuscularly every 4 hours) caused the bleeding to subside. In 2 patients ecchymotic areas were noted about the sites where blood was drawn for the daily prothrombin determinations during a period when the prothrombin times were reported as "no clot". This appeared to be another sign to be considered in seeking clinical evidence of anticoagulant toxicity. Thirteen patients with extremely prolonged prothrombin times ("no clot") at some time in the study had no evidence of hemorrhagic tendencies. Nausea and vomiting soon after administration of Tromexan were occasionally observed.

Case Reports. One patient received Tromexan despite a moderate degree of renal insufficiency and developed toxic hemorrhagic tendencies. The following is a brief summary of the case:

Case 26. J. McG., a 63-year old white male, was admitted with acute embolization of the left popliteal artery of 2 days' duration and arteriosclerotic heart disease with mild congestive failure. In view of the patient's poor condition and the 2-day delay in hospitalization, the surgical service was hesitant in doing an embolectomy and advised conservative therapy.

The laboratory studies disclosed the following: urinalysis 3 + albumin, many white blood cells, moderate red blood cells, casts and pus clumps. The blood urea nitrogen was 53 mg. per 100 cc. The hemogram was within normal limits except for a white blood count of 20,250.

Since the patient's condition was desperate, anticoagulant therapy was instituted despite the renal insufficiency as estimated by the urinalysis and the nitrogen retention. Following an initial administration of 1,500 mg. of Tromexan, the prothrombin time rose to 27 seconds (control 14 seconds, Thromboplastin A) within 24 hours. A second dose of 900 mg. was administered resulting in an inability to form a clot in the prothrombin time determinations for 3 consecutive days. On the 7th day after the first administration of Tromexan the prothrombin time gradually decreased to normal levels. Three days after the initial dose of Tromexan the patient developed epistaxis, a watery stool containing blood, and an increase in microscopic hematuria. The blood urea nitrogen at this time had increased to 122 mg. per 100 cc. Dry gangrene with demarcation developed and on the 7th day a mid-thigh amputation was performed.

This illustrates one of the most important contraindications to anticoagulant therapy: namely, renal insufficiency and failure. The toxic manifestations are clearly illustrated by the epistaxis, bloody stool, and an increase in microscopic hematuria.

The following brief case reports have been included to illustrate a few of the problems which were encountered during anticoagulant therapy.

Case 25. T. D., a 67-year old white male, was admitted with diabetes mellitus and gangrene of the right foot necessitating a mid-thigh amputation. The diabetes was well controlled and the blood sugar remained within the range of estimated normal throughout the hospital course. Postoperatively, the patient developed showers of small pulmonary emboli. Tromexan was instituted with an initial dose of 1,500 mg. Subsequent daily dosages ranged between 1,200 and 2,700 mg. with absolutely no significant change in prothrombin time from the patient's initial control. A total of 26,300 mg. was administered in 17 days, or an average of 1,550 mg. daily. The patient recovered completely and was discharged on the 61st hospital day.

The above case illustrates the occurrence of unusual resistance to Tromexan. Whether this was due to poor absorption, improper utilization, excessively rapid excretion of the preparation or due to some unusual metabolic disturbance remains unknown.

Case 16. S. P., a 67-year old white male, was admitted with an acute myocardial infarction. Repository heparin and Tromexan were administered upon admission. At the beginning of the 5th week of treatment after

300 mg. of Tromexan had been given, resulting in a prothrombin time of 28 seconds (control 15 seconds, Thromboplastin A), a tooth was extracted because of severe oral pain. The Dental service contemplated marked hemorrhage after extraction because of extensive calcareous deposits around the teeth at the gum line. After the extraction slight oozing of blood occurred for 12 hours. Tromexan was discontinued and no signs of bleeding were noted after 24 hours, when the packing was removed. The prothrombin time returned to pretreatment levels within 24 hours.

This case illustrates several points: 1) the rapidity of Tromexan excretion, 2) The rapid return of prothrombin time to normal after discontinuance of therapy, and 3) bleeding due to factors other than hypoprothrombinemia.

Discussion. TROMEXAN. This study corroborates the reports which have appeared in the literature, namely, that Tromexan is more soluble, more readily absorbed, excreted more rapidly, and less toxic than other dicoumarin preparations[2,4,5,13]. The metabolic route of excretion of the drug is still under investigation[7].

Reinis and Kubik, studying the pharmacology of Tromexan, administered a single dose of 900 mg. In patients who responded well a measurable prolongation of the prothrombin time occurred within 1 or 2 hours, reaching a maximum in 24 to 48 hours[12]. Burke and Wright, in their studies of 24 normal individuals who received a single dose of 1,500 to 1,800 mg. of Tromexan, were unable to show an appreciable prolongation of the prothrombin time in 6 hours; however, with undilute plasma, the prothrombin time was prolonged consistently and uniformly reached a level of 20 to 30 seconds (undilute) in 24 hours. Following the single administration, the prothrombin time returned to normal within 48 to 60 hours[3].

Our experience with Tromexan has indicated that the majority of patients will require an initial dose of 1,500 to 1,800 mg., which is approximately 5 to 6 times that of Dicumarol, in order to elevate the prothrombin time to therapeutic levels in 24 hours. Lower dosages ranging from 900 to 1200 mg. will usually cause a lesser response. In no instance were therapeutic levels reached in 24 hours.

In the management of patients under treatment with Tromexan, daily prothrombin determinations are essential. This is especially true in the first 7 days of therapy when wide fluctuations of the prothrombin time occur. Similar observations have been made by Solomon[15] and Barker *et al.*[1]. After the first 7 days, less fluctuation of prothrombin times was noted, but mild cumulative phenomena were found at some time during therapy in 15 cases of this study. A single daily dose appeared to be satisfactory in most instances; however, in those cases in which marked individual idiosyncrasies to the drug were observed, as evidenced by continuous irregularities in the prothrombin times, divided dose schedules may be preferable[3,5,15]. Occasionally a highly resistant individual will be encountered (Case 25, T. D.). The omission of a single daily dose when needed will frequently upset the entire schedule due to the rapid dissipation of the hypoprothrombinemic effect. In general, an arbitrary therapeutic level of 2 to 2½ times the normal control prothrombin time (28 to 45 seconds for whole plasma) was considered adequate.

The major contraindications to dicoumarin preparations, including Tromexan, are hemorrhagic diseases, hepatic dysfunction, renal insufficiency and failure, severe vitamin deficiency and cachectic states, toxic-infectious syndromes, menstruation, ulcerating or granulomatous lesions, bacterial endocarditis, preoperative and postopera-

tive neurosurgical conditions, and prospective surgery. The drug should be used cautiously in patients with proved cerebral embolism and thrombosis. All other possible causes for cerebral vascular accidents, such as head injuries, should be ruled out before instituting this type of therapy.

The major toxic manifestations observed in this study were those related to bleeding phenomena, especially microscopic hematuria, but no serious hemorrhage occurred. The hemorrhagic tendencies encountered during anticoagulant therapy in all probability do not depend only on hypoprothrombinemia. Thirteen cases were observed in which no clot formed during prothrombin time determinations and yet no bleeding phenomena occurred. Other factors in the blood coagulation mechanism, such as local capillary contractility, platelet count and stability, plasma vitamin C levels, fibrinogen levels, blood calcium levels, and other unknown factors in the blood coagulation mechanism, may all be closely concerned in those cases with bleeding tendencies.

Tromexan, although not the ideal anticoagulant, has certain advantages and disadvantages when compared to other dicoumarin preparations. The greatest advantage in this study appears to be the low incidence of toxicity observed and the rapid excretion of the drug. No deaths occurred which could be attributed to Tromexan. This is in sharp contrast to our experience and the experience of others[6]. We have personally observed in a comparable number of patients 2 fatalities directly attributed to Dicumarol toxicity. Both deaths were due to massive hemorrhage, one being a retroperitoneal hemorrhage and the other a mediastinal hemorrhage.

The greatest disadvantage of the preparation was the marked fluctuation of the daily prothrombin times and the resultant inability to maintain individual cases at constant therapeutic levels.

Vitamin K. The value of an agent which will combat the hemorrhagic phenomena occasionally observed during anticoagulant therapy without necessitating the use of blood or plasma is self-evident when one considers the added dangers of homologous serum jaundice which may be encountered.

A review of the literature shows that various authors have placed emphasis on the superiority of one or another of the parenteral Vitamin K preparations[3-8,10,11]. In this study 2 proprietary water soluble Vitamin K preparations were utilized. Our results in a limited number of cases selected at random revealed that the water soluble preparations definitely decreased prothrombin time in seconds in those cases with normal hepatic and renal function. Vitamin K appears to compete with Tromexan in those patients receiving both drugs simultaneously. However, if a sufficient amount of Vitamin K is administered, the Vitamin K overcomes the effect of the dicoumarin preparation and a decrease in prothrombin time in seconds results. These observations are in agreement with those of Burke and Wright[3], who noted a return of prothrombin time to normal limits in 12 hours after administration of water soluble Vitamin K, and also with those of Barker *et al.*[1], who noted lowering of prothrombin time after 16 to 20 hours with water soluble preparations of Vitamin K. Further studies on this phase of anticoagulant therapy are indicated, inasmuch as the rapidity of Tromexan excretion and destruction must be taken into account in evaluating the effectiveness of any Vitamin K preparation.

Despite the apparent effectiveness of water soluble Vitamin K, if the hemorrhagic tendencies are not con-

trolled rapidly by adequate doses of the preparation given intravenously, one should not hesitate to administer freshly citrated whole blood or fresh plasma.

Prothrombin Times. The efficiency and safety of any course of anticoagulant therapy depends to a great extent on a reliable method of performing and reporting prothrombin time.

Early in the study it became apparent that the reporting of prothrombin time on a percentage basis, as computed from a curve constructed by plotting serial plasma dilutions against prothrombin time in seconds, was not as accurate as the direct comparison of the prothrombin time in seconds of the patient to that of a standard control performed at the same time. The resultant curves (Fig. 1) are based on averages which have a wide latitude and are dependent on the thromboplastic substances utilized. Although plotted curves are similar in contour to those of both thromboplastin substances employed in this study, they are not identical and inaccuracies are inevitably introduced. At times it may be noted that the curves of each preparation may cross each other or coincide at various points.

The concept of inaccuracies in conversion of seconds to % is in agreement with the observations of Overman, Sorenson, and Wright[11], who are of the opinion that "the conversion of prothrombin time in seconds to percentage prothrombin is not a valid manipulation and only confuses the consideration of the problem." Shapiro and Weiner[14] also prefer to report the prothrombin time in seconds.

Furthermore, it was noted that the simplest techniques used in performing the prothrombin time determinations gave, in general, the most accurate results. Thromboplastin A gave uniform control levels and less variations in prothrombin time in patients under treatment than did Thromboplastin B. This could best be explained by less error in laboratory technique when Thromboplastin A was used as well as rigid standardization of the preparation.

Tromexan and Dicumarol. This study was not intended to be a comparative one as to the efficacy of Tromexan and Dicumarol. However, between 1949 and 1951 a comparable number of patients was treated with Dicumarol under similar conditions with the exception of prothrombin time determinations, which were performed with other thromboplastic substances. This omission makes a strict comparative study of the 2 preparations impossible.

From our experience with Tromexan and Dicumarol the following factors are evident:

1. Both medications give cumulative phenomena; however, these effects are dissipated more rapidly in those patients receiving Tromexan either when the drug is omitted or when water soluble vitamin K preparations are administered.

2. Maintenance of therapeutic levels was more difficult in patients receiving Tromexan, but these effects were overshadowed by the relative safety of the drug.

3. Macroscopic and microscopic hematuria was observed more frequently in dicoumarolized patients. Two fatalities occurred in patients treated with Dicoumarol.

4. Patients receiving Tromexan attained therapeutic prothrombin time levels more rapidly than those patients receiving Dicumarol.

The conclusion reached, after weighing the above factors, is that Tromexan appeared to be a safer and in many respects a more advantageous preparation than Dicumarol. However, it is emphasized that at present there is no

ideal anticoagulant, and many considerations from both the clinical and the laboratory standpoints must be evaluated before an anticoagulant preparation is chosen.

Summary. 1. A study of 50 cases treated with the anticoagulant Tromexan is reported.

2. The optimal initial dose of Tromexan which resulted in therapeutic levels of prothrombin time within 24 hours was found to be 1,500 to 1,800 mg. Subsequent daily doses ranging from 300 to 900 mg. depended on the patient's response to the drug as evidenced by daily prothrombin time determinations. It is advocated that the prothrombin time be reported in seconds with the control time and preparation used noted, rather than as a percentage of normal prothrombin activity.

3. No serious toxic manifestations were noted in this study. Microscopic hematuria was observed in 8% of the cases treated. Ecchymotic areas at the site of blood withdrawal for daily prothrombin time determinations were observed to be a readily detectable clinical sign of toxicity.

4. Intravenously or intramuscularly administered water soluble vitamin K preparations appear to combat effectively the hypoprothrombinemic effects of Tromexan.

5. Tromexan appeared to be a safer and in many respects a more advantageous preparation than Dicumarol.

6. From the above studies it is concluded that Tromexan is a drug which can be administered safely provided accurate daily prothrombin time determinations are performed, although it must be understood that marked daily fluctuations of the prothrombin time are to be expected despite careful regulation of the preparation. The importance of reliable thromboplastic substances such as Thromboplastin A is emphasized.

The authors are indebted to Dr. Murray W. Shulman, Assistant Pathologist of the Newark City Hospital, for his aid in the problems encountered in this study as well as his many helpful criticisms and instruction. They are also indebted to the technicians of the Hematology Laboratory of the Newark City Hospital; to the entire attending and house staff of the hospital who referred to them cases for anticoagulant therapy; and to Dr. William T. Strauss, and Mr. Neil Stasilli, Medical Director and Statistician, respectively, of the Chilcott Laboratories, Division of the Maltine Company. The latter prepared Figs. 1 and 2.

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EFFECTS OF THE INTRAVENOUS ADMINISTRATION OF GELATIN SOLUTION (10%)

A Laboratory Study on 24 Patients with Chronic Disease

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Although gelatin solutions were first administered intravenously in 1897, by Dastre and Floresco, in an attempt to increase the coagulability of the blood after hemorrhage[45], this substance was soon abandoned because of the unsatisfactory preparations then available. More thorough and detailed investigations had to await the development of better physico-chemical and bacteriologic methods which made it possible to prepare pure, stable, sterile solutions for intravenous use. During the past decade, and particularly during the war years, numerous investigators published reports on experimental animals and on clinical subjects. Most of these studies were directed toward establishing the value of gelatin solutions as a substitute for plasma, especially in hemorrhagic shock. The consensus is that gelatin solutions, administered intravenously, have a definite, though limited, usefulness in restoring the blood volume in acute shock from hemorrhage or burns, and merit clinical consideration as an immediate emergency treatment in such cases. Studies to determine the value of gelatin as a nutritional agent in cases of malnutrition and hypoproteinemia have yielded far less conclusive findings. There is also still considerable discrepancy in reported findings and opinion as to the retention and excretion of gelatin following intravenous injection.

The present study was undertaken with the hope of assembling some data that might be useful and helpful in clarifying some of these problems. However, the results are not nearly so definitive as would be desirable. Even though the findings do not permit clear-cut conclusions regarding the metabolism of gelatin, it seems worth while to report the data in detail, so they may be available to others who may be interested in a similar research.†

The purpose of this study was to administer a 10% solution of gelatin to patients chronically ill with malnutri-

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† All the laboratory tests were made by the same technician, who is extremely well trained and reliable, after a comparative check of numerous methods, with selection of those that proved most accurate in her hands.

tion, liver dysfunction, and edema, and to determine its retention in the blood stream and its excretion in the urine over a 48-hour period, with the hope of elucidating the indications for its use and its clinical value in supportive treatment as a substitute for whole blood or plasma. Approximately half the patients studied had hepatic disease, and a particular point of the investigation was to ascertain the effect of gelatin in patients with ascites and edema.

Materials and Methods. Twenty-four patients with various chronic diseases, including hepatic disease, arteriosclerosis, malnutrition, pulmonary affections and renal disease, received an intravenous injection of 500 cc. of a 10% solution of gelatin prepared from beef bone collagen. †

The day before the infusion was carried out, each patient was subjected to the following laboratory tests: hemoglobin determination, hematocrit, total protein in the blood along with the albumin and globulin fractions, nonprotein nitrogen, blood volume, bromsulphalein retention, and the cephalin flocculation test. After the infusion, total protein, nonprotein nitrogen, hemoglobin and hematocrit, as well as determinations of the gelatin in the blood and urine and measurement of urine volume were made at the conclusion of the injection, and 6, 24, and 48 hours later. Determinations of the blood volume, bromsulphalein retention, and cephalin-cholesterol flocculation were made immediately after the injection. Protein in the urine was determined in 3 patients with evidence of renal damage (Cases 8, 23, and 24). Determination of sedimentation rates was omitted, since all investigators have reported an increase in sedimentation of erythrocytes following the parenteral administration of gelatin.

Janota's method[17] was used in the determination of gelatin in the blood and urine. Nitrogen was determined according to the micro-Kjeldahl method described by Hiller, Plazin and Van Slyke[11]. The separation of nonprotein nitrogen from gelatin and protein nitrogen was performed according to the procedure of Little and Wells[31]. Howe's method was used in the determination of globulin[14]. Barker's[1] urea method was employed. Other procedures used were: blood volume, Mitshe and Cohen[35]; bromsulphalein, Gaebler[8]; cephalin-cholesterol flocculation, Hanger[10].

Results. The results of these studies are shown in detail in Tables 1 to 6. The findings are, for the most part, negative, and do not furnish the information we were seeking regarding the metabolism of gelatin injected into the blood stream. There was no change that can be interpreted as significant in the total blood protein, nonprotein nitrogen, or in the liver function, as indicated by bromsulphalein retention and the cephalin-cholesterol flocculation tests. There were some changes in the urea clearance before and after the gelatin injections, but the significance of these is difficult to evaluate; in some instances there was an increase and in others a decrease.

The gelatin apparently disappeared rapidly from the blood, with only small amounts (0.1 gm. per 100 cc. or less) remaining at the end of 48 hours. The gelatin disappeared rapidly from the urine, too, with no measurable quantity detected 48 hours after the injection, in the majority of cases. The average total excretion in the urine during the first 24 hours in 23 cases* was 14.4 gm., with the largest amount 20.5 gm. and the lowest 7.6 and 7.9 gm., respectively. The high value was obtained in a case of cirrhosis and pulmonary emphysema (Case 21). One of the patients with the lowest excretion during the first 24 hours had diabetic neuropathy with edema (probably owing to kidney damage) and the other had kidney disease with edema. It is interesting to note that in these 2 patients (Case 8 and Case 23) and one

† The gelatin used in this study was furnished by the Upjohn Company of Kalamazoo, Michigan.

* The tests were not completed in one case.

TABLE 1.—CLINICAL DATA, ALBUMIN, GLOBULIN AND TOTAL PROTEIN OBSERVATIONS IN 24 PATIENTS GIVEN 500 CC. OF A 10% GELATIN SOLUTION INTRAVENOUSLY

Case Diagnosis	Sex	Age	Weight lb.	Time for Injection	Albumin gm. per 100 cc.	Globulin gm. per 100 cc.	Total Protein (gm. per 100 cc.)				
							Before	End	6 hr.	24 hr.	48 hr.
1. Malnutrition	F	77	110	3 hr.	3.6	1.9	5.5	3.9	4.9	5.4	5.0
2. Malnutrition, pulmonary emphysema, arteriosclerosis	M	72			3.1	3.8	6.9	5.8	6.2		6.65
3. Arteriosclerosis	M	63		4 hr., 15 m.	4.3	2.9	7.2	6.25	5.8	7.1	6.8
4. Carcinoma of larynx; diabetes	M	60	132		4.2	2.4	6.6	5.8	6.1	6.4	6.7
5. Bronchogenic carcinoma with metastases	M	60	122	3 hr., 30 m.	3.6	3.4	7.0	6.4	6.6	6.7	7.5
6. Neoplasm	M	59	148	3 hr., 15 m.	3.6	3.2	6.8	6.0	6.3	7.0	7.3
7. Dorsolateral spinal degeneration	M	45	134	3 hr., 30 m.	4.9	2.7	7.6	5.8	6.0	6.5	6.5
8. Diabetic neuropathy	F	58	130	3 hr.	2.6	2.6	5.2	4.0	4.6	5.0	4.4
9. Cellulitis	M	44	140	3 hr., 30 m.	3.8	3.2	7.0	6.4	6.3	7.3	7.1
10. Pleural effusion	M		125	2 hr., 30 m.	4.2	4.1	8.3	6.4	7.6	7.8	8.6
11. Lung lesion	M	62	178	5 hr., 30 m.	5.5	2.8	8.3	7.0	6.9	7.4	7.5
12. Pneumonia	M	39	110	3 hr., 15 m.	3.6	4.0	7.6	6.4	6.4	6.5	6.5
13. Laennec's cirrhosis	M	40	143	2 hr., 45 m.	3.0	3.6	6.6	5.7	5.9	6.1	7.3
14. Laennec's cirrhosis	M	44	153	2 hr., 15 m.	4.3	4.0	8.3	7.2	8.0	8.5	8.1
15. Hepatomegaly; prob. Laennec's cirrhosis	M	63	130	3 hr.	4.0	3.6	7.6	6.5	7.2	7.0	7.4
16. Laennec's cirrhosis	M	53	167	3 hr., 20 m.	2.0	4.3	6.3	4.9	5.4	5.8	5.9
17. Cirrhosis	M	46	232	3 hr., 20 m.	3.3	4.9	8.2	8.1	8.3	8.3	9.0
18. Laennec's cirrhosis	M	55	144	3 hr., 15 m.	3.2	3.0	6.2	5.2	5.4	5.9	5.9
19. Liver disease; prob. cirrhosis	M	72	124	2 hr., 45 m.	2.4	4.2	6.6	5.0	5.7	5.8	6.4
20. Alcoholism; cirrhosis	M	49	185	3 hr., 40 m.	4.0	4.0	8.0	7.7	7.9	7.4	7.7
21. Cirrhosis	M	63	133	3 hr., 15 m.	4.0	4.2	8.2	6.8	7.0	7.5	Patient discharged
22. Alcoholism; possible liver disease	M	36	115	3 hr., 15 m.	3.6	3.1	6.7	5.5	5.5	6.6	7.4
23. Kidney disease with edema	M	65	169	3 hr.	2.2	2.3	4.5	3.5	3.7	4.6	5.1
24. Intercapillary glomerulosclerosis; diabetes mellitus	M		180	3 hr., 30 m.	2.1	2.3	4.4	3.8	4.4	4.3	4.5

other (Case 24) with diabetes and intercapillary glomerulonephrosis with edema, the excretion of gelatin in the urine at the conclusion of the injection was low and increased during the 48-hour period of study, while in the other cases there was a progressive decrease, with the highest amount excreted at the end of 24 hours. In the last 2 cases (with kidney disease) there was also relatively high excretion at the end of 48 hours, 3.4 and 6.2 gm., respectively.

Since the total amount of gelatin excreted in the urine in 48 hours was less than one-third the quantity of 50 gm. which was injected, the evidence indicates that two-thirds, or more, of the gelatin is retained by the body beyond this period. There has been some speculation that gelatin may be retained in the liver, but if so, it does not produce any change in liver function as shown by the tests of bromsulphalein retention and cephalin-cholesterol flocculation. The evidence of this study would suggest that the gelatin is probably stored in other tissues.

There was usually a decrease in the hematocrit at the end of the injection and 6 hours afterward, with a return to the pre-injection level at 24 and 48 hours.

The blood volume determinations showed an increase in both plasma volume and total volume in all but one

TABLE 2.—NONPROTEIN NITROGEN AND UREA CLEARANCE IN 24 PATIENTS GIVEN 500 CC. OF A 10% SOLUTION OF GELATIN INTRAVENOUSLY

	Nonprotein Nitrogen (mg. per 100 cc.)					*Urea Clearance (cc.)*	
Case	*Before*	*End*	*6 hr.*	*24 hr.*	*48 hr.*	*Before*	*After*
1	18	19	17	29	29	8	7
2	28	35	32		30		
3	25	27	31	33	30	35	38
						27	
4	33	32	37	32	27	37	63 (maximal)
							40
5	61	60	52	51	55	Patient uncooperative	
6	34	32	32	33	31	60	25
						60	28
							24 (second week)
							24
7	26	26	25	33	23		
8	67	71	71	73	79	21 (maximal)	12 (standard)
						16 "	
9	30	32	32	32	32		
10	33	27	31	31	31		
11	29	33	32	36	36		
12	23	26	28	23	23	59	31
							35
13	41	41	49	48	50	15	37
						16	36
14	30	36	38	39	28	20	55
						31	43
15	24	26	28	27	29	45	
						46	
16	35	37	36	35	34	56	57
						59	50
17	24	27	28	25	25	58	51
						52	52
18	26	25	26	29	24	25	36
						48	46
19	36	31	31	43	45	9	26
						13	23
20	27	25	28	29	25	47	70
						83 (maximal)	61
21	23	23	25	25		17 "	
						33 "	
22	14	16	19	19	18	41 "	57 (maximal)
							51 "
23	45	46	50	49	51		
24	67	73	73	78	83		

case, immediately after the injection, as would be expected. Urine volumes were increased after 24 hours in practically all the cases, and in the majority, the diuresis apparently was sufficient to be of clinical significance. The increase in urine volume was most striking in the patients with edema of renal origin (Cases 8, 23, 24). It was less prominent in patients with cirrhosis and ascites. Unfortunately, the patients were not weighed on the days succeeding the injection, so this check is not available in evaluating the significance of the increased urine output.

Most of the patients felt that they were subjectively improved after the injection of the gelatin. This improvement was particularly striking in Case 24. This patient, who had diabetic glomerular intercapillary sclerosis, demonstrated such an encouraging response to the initial injection that 4 additional infusions were given on succeeding days. The urine volume was determined 24 hours after each injection and showed 2850, 1520, 1540, and

TABLE 3.—DATA ON HEMOGLOBIN AND HEMATOCRIT IN 24 PATIENTS GIVEN 500 CC. OF A 10% SOLUTION OF GELATIN INTRAVENOUSLY

	Hemoglobin (gm. per 100 cc.)					*Hematocrit (%)*				
Case	*Before*	*End*	*6 hr.*	*24 hr.*	*48 hr.*	*Before*	*End*	*6 hr.*	*24 hr.*	*48 hr.*
1	13.6	11.2	12.4	13.2	12.0	41	32	39	41	39
2	16.4					47				
3	14.5	14.5	14.5	15.4	15.4	44	42	39.5	44	44
4	14.9	13.4	13.6	13.6	14.1	44	37	38.5	40	40
5	12.0	11.2	11.6	12.0	12.4	35.5	32	35	36	36.5
6	12.8	12.0	14.1	14.1	13.2	38	35	39	39	40
7	Not done					Not done				
8	12.8	11.2	12.8	13.2	10.5	35	30	36	37	32.5
9	14.3	14.3	14.1	15.8	15.4	41.5	41.5	41	44	44
10	Not done					Not done				
11	Not done					Not done				
12	15.8	11.6	12.8	12.0	12.4	49	39	41	41	40
13	10.1	9.0	9.4	10.1	10.5	32	29	30	30.5	33
14	9.4	8.4	10.1	11.2	9.4	28	26	31	32	29
15	14.5	12.0	14.1	14.5	14.5	45	38	43	42	44
16	16.8	13.6	14.3	14.9	14.9	51	43	46.5	49	50
17	14.1		13.2	14.5	14.6	41.5		40	42.5	42
18	9.4	9.4	9.4	9.4	9.4	30	29	29.5	30	30.5
19	8.0	6.7	8.4	7.7	9.4	24.5	21	26	20	28.5
20	16.4	15.4	15.8	14.5	16.4	47.5	43	45	43	45
21	14.1	13.2	13.2	14.1		42.5	38	40.5	42	
22	12.8	11.2	10.9	11.2	11.2	37	32.5	34	34	35
23	9.4	6.7	8.0	10.1	10.1	28.5	21	24	29.5	30
24	8.7	7.4	9.0	9.0	9.0	27	23	28	27	27

TABLE 4.—BLOOD GELATIN AND URINE GELATIN IN 24 PATIENTS GIVEN 500 CC. OF A 10% GELATIN SOLUTION INTRAVENOUSLY

	Blood Gelatin (gm. per 100 cc.)				*Urine Gelatin (gm.)*			
Case	*End*	*6 hr.*	*24 hr.*	*48 hr.*	*End*	*6 hr.*	*24 hr.*	*48 hr.*
1	1.0	0.9	0.5	0.23	5.4	5.4	2.0	1.1
2	0.89	0.56		0.16	2.1	14.8		
3	0.69	0.4	0.25	0.11	10.9	6.7	1.8	None
4	0.8	0.53	0.3	0.15	5.5	10.5	0.5	None
5	0.49	0.3	0.13	0.05	4.9	4.9	None	None
6	0.56	0.35	0.08	0.03	6.0	5.5	2.7	None
7	0.83	0.49	0.28	0.13	9.7	3.9	3.4	
8	0.88	0.65	0.39	0.2	1.5	2.0	4.4	2.0
9	0.6	0.38	0.22	0.09	7.2	7.4	0.9	None
10	0.69	0.42	0.2	0.05	7.5	1.7	1.8	0.3
11	0.47	0.32	0.15	0.04	11.3	2.5	3.5	1.9
12	0.9	0.57	0.29	0.1	8.0	7.5	0.5	
13	0.63	0.42	0.16	0.04	5.0	3.5	2.7	None
14	0.51	0.25	0.11	0.02	9.2	5.0	1.0	None
15	0.74	0.43	0.2	0.07	7.8	5.5	4.9	None
16	0.67	0.45	0.25	0.12	8.8	6.9	1.7	1.1
17	0.43	0.2	0.06	None	8.6	5.0	2.9	None
18	0.6	0.38	0.2	0.07	10.0	3.4	0.9	None
19	0.8	0.54	0.22	0.12	3.7	4.6	3.8	
20	0.55	0.29	0.11	None	6.6	4.8	1.0	None
21	0.79	0.46	0.2		8.8	7.8	3.9	
22	0.79	0.44	0.25	0.1	8.2	3.3	2.5	None
23	0.7	0.5	0.36	0.25	0.9	3.1	3.6	3.4
24	0.52	0.39	0.22	0.12	1.8	2.0	8.0	6.2

TABLE 5.—URINE AND BLOOD VOLUMES AND LIVER FUNCTION TESTS IN 24 PATIENTS GIVEN 500 CC. OF A 10% GELATIN SOLUTION INTRAVENOUSLY

	Urine Volume (cc.)				*Blood Volume (cc.)*				*Bromsulphalein Retention (%)*		*Cephalin Flocculation*	
					Before		*After*					
Case	*End*	*6 hr.*	*24 hr.*	*48 hr.*	*Plasma*	*Blood*	*Plasma*	*Blood*	*Before*	*After*	*Before*	*After*
1	830	1000	1620	750	1909	3235	Unsuccessful		37		2+	
2	100	260										
3	780	450	1250	3030	2930	5232	5280	9103	4	8	Negative	Negative
4	280	750	1110	1220	2148	3836	3056	4851	3	9	Negative	Negative
5	105	125	320	500	4230	6558	5409	7954	4		3+	3+
6	200	245	815	1185	2777	4480	4230	6508	2	7	Negative	2+*
7	680	260	600									
8	240	250	1570	1475	Not done				1	1	Negative	Negative
9	330	470	1070	1210	3019	5489	3688	6304	6		Not done	
10	475	250	220	940	Not done				Not done		Not done	
11	1025	500	850	1450	Not done				Not done		Not done	
12	305	250	1680		Not successful (sample lost)					6		Negative
13	325	78	440	940	Not done				32	33	Negative	Negative
14	115	120	450	800	3688	5122	4494	6073	17	16	3+	3+
15	105	210	1670	1800	2560	4654	3122	5035	12		2+	
16	260	215	570	725	2777	5667	4230	7421	46	47	3+	3+
17	320	275	1730	2770	7207	12320#	4589	7642	23	16	3+	3+
18	500	135	390		3695	5278	3695	5204	18	16	3+	3+
19	170	105	200		3122	4135	3912	4952	27	36	Negative	Negative
20	305	320	1770	1480	3540	6743	4061	7125	13	13	3+	2+
21	550	260	525		2511	4367	2251	3631	16		2+	
22	163	95	985	1935	Unsuccessful				6	1	Negative	Negative
23	430	700	940	2550	3801	5316	4643	5877	1	2	Negative	Negative
24	565	550	2300	2550	4494	6156	6433	8354	1	1	Negative	Negative

* Negative second week after gelatin injection.
\# Determination evidently in error.

TABLE 6.—URINE PROTEIN IN 3 PATIENTS WITH EDEMA OF RENAL ORIGIN GIVEN 500 CC. OF A 10% GELATIN SOLUTION INTRAVENOUSLY

	Case 8		*Case 23*		*Case 24*	
	Urine Volume cc.	*Urine Protein gm.*	*Urine Volume cc.*	*Urine Protein gm.*	*Urine Volume cc.*	*Urine Protein gm.*
End	240	2.1	430	1.4	565	1.8
6 hr.	250	2.5	700	3.3	550	1.4
24 hr.	1570	14.0	940	6.0	2300	8.0
48 hr.	1475	11.3	2550	7.7	2550	6.2

1115 cc. (1165 cc. after 48 hours) on these occasions.

Comment. Although the number of patients studied was too small and the data obtained were too equivocal to permit any sweeping conclusions, the findings of this study tend to confirm and extend the observations of Koop and his collaborators[21,23,24] as to the effect of gelatin solutions on patients with edema and ascites. This group from the University of Pennsylvania has reported that in their experience the diuretic effect of gelatin is most pronounced in patients with nephrosis. They have observed some response, though not a consistent one, in patients with ascites, and very little effect in patients with nephritis. Koop's studies and those reported here suggest that additional investigation of the possible role of gelatin in producing diuresis in certain types of cases, particularly those with hypoproteinemia, may be desirable. Experiments with gelatins of various molecular weights and in varying concentrations should be tried to determine, if possible, the best preparation for this purpose. Koop[21] found that the large molecular gelatin produces greater diuresis than the gelatin of small molecular type.

In our studies, we used a more concentrated solution, 10%, than the majority of other workers have employed. Most of them have administered solu-

tions containing 4 to 6% of gelatin. The higher concentration we used may possibly account for the apparently greater retention of gelatin by the patients in our series. The amount of gelatin they excreted in the urine during the first 48 hours was less than that observed by some other authors. The total amount excreted in the urine during the first 48 hours has been reported to be as high as 80%, whereas in our patients, 30% or less was recovered in the urine during a similar period.

Discussion. The numerous investigations that have been made on the intravenous use of gelatin have established some facts about this substance and have resulted in the production of refined, non-toxic products which are safe for clinical administration. Nevertheless, numerous questions remain unanswered as to the utilization and excretion of gelatin in man and concerning the indications for its use in the treatment of patients, and the optimal technique of administration.

The major portion of the studies published during the last 10 years have dealt with experiments on animals[2-5, 9,13,15,18-20, 26-30,33,34,36,38,42,43], particularly on the control of hemorrhagic shock. This experimental work has been done chiefly by teams of investigators at research centers, such as Princeton University[19,42,43], University of Louisville[9, 13,20,26,27], Bowman Gray Medical School[2,29,30], University of Rochester[34,38], University of Pennsylvania[21,23, 24,36], Michael Reese Hospital, Chicago[18,28,33], Northwestern University Medical School[15] and the University of Chicago[3,5].

These experiments have demonstrated conclusively the value of gelatin solutions in restoring the circulating blood volume and in controlling the symptoms of hemorrhagic[9,15,18,26-28, 33,34,36] and other types of shock[19,30,42,43]. Various types of gelatin in varying concentrations have been used in these experiments, but all, excepting a 2% solution, proved effective in restoration of blood pressure and blood volume in animals suffering from shock. There is general agreement that gelatin solutions are more effective than saline and glucose solutions for this purpose, but somewhat inferior to plasma or whole blood. The Princeton group has reported that intermittent administration over a 7 or 8 hour period was more effective than a single large infusion[19,42,43]. In experimenting with gelatin preparations of various molecular weights, Knoefel and Lehmann[29] found that the retention of gelatin in normal dogs varies with the molecular weight, but does not increase markedly with molecular weights above 50,000. The fraction of injected gelatin excreted in the urine during the first 4 hours varies inversely with the molecular weight. Those who have experimented with solutions of varying concentrations usually report greater retention of gelatin with more concentrated solutions (6 to 10%) than with those less than 5%[9,28,29].

Brunschwig and his collaborators[3,5] conducted experimental studies of nitrogen balance in dogs maintained on a low protein diet, to determine the possible nutritive value of intravenous gelatin. Daily injections of 150 to 250 cc. of a 10% gelatin solution were administered for several days, followed by a period of observation without gelatin injections. In 3 of 4 dogs, nitrogen balance was maintained after cessation of gelatin injections, suggesting that all the gelatin was not immediately excreted. One dog refused to eat after the 7-day period of gelatin injections and went into marked negative nitrogen balance. An increase in nonprotein nitrogen was noted following the injections. A similar finding was reported in experiments by Janota and her collaborators[18]. In 6 patients with advanced car-

cinomatosis to whom Brunschwig, Corbin and Johnston[3] gave gelatin intravenously, there was an increase in urea nitrogen excretion during and/or following the injections. In a later report on the clinical use of gelatin injections, Brunschwig and Nichols[4] reported results on 23 patients. In 17 patients receiving one injection of 400 to 800 cc. of 8% gelatin solution, there was appreciable retention of gelatin in 11 and little or no retention in 6. In 6 patients receiving repeated daily injections, there was some retention of gelatin in all: 40 to 43% of the gelatin was retained and 60 to 75% was recovered in the urine. The relative amount retained was approximately the same, whether 1 or 8 daily injections were made.

Another experiment on the nutritional value of gelatin solutions was reported by Robscheit-Robbins, Miller and Whipple[38] on dogs that were both anemic and hypoproteinemic (doubly depleted). They concluded that gelatin given by vein to such dogs gives no immediate toxic response and no anaphylactoid reactions and may contribute something to the building of new hemoglobin and plasma protein. Gelatin given by vein during 1 or 2 weeks (total 3 to 17 gm. per kg.) usually causes serious disturbances: inhibition of blood protein production, signs of intoxication, much weight loss, and even death. Gelatin given by vein for 2 to 3 days (total 1 to 3 gm. per kg.) may not cause any recognizable abnormalities, but dogs vary greatly in their individual response. Some may tolerate a total of 7 gm. per kg. without significant disturbance and others may be seriously intoxicated by 2 to 3 gm. per kg. There is no way of predicting which animal will be less tolerant. Where the gelatin by vein inflicts its damage is not clear, but these authors feel that the disturbance of blood protein implicates the liver. Gelatin of smaller molecular weight proved no less toxic than standard gelatin. The final conclusion of this study was that gelatin by mouth may contribute to, but cannot alone support, the production of new hemoglobin and plasma protein. The implications are that when gelatin is used in clinical cases the amount given should be carefully controlled.

There is general agreement that properly prepared gelatin in appropriate dosage is safe for intravenous use and has no anaphylactic effect. In some of the work reported, there has been some complaint of thrombosis at the site of injection, but this has been attributed largely to the preservatives used. This difficulty has been corrected in the material prepared more recently. The increased sedimentation of erythrocytes and the tendency to pseudo-agglutination caused by gelatin infusions have been quite consistently cited. To overcome the practical difficulties involved in this phenomenon, Koop and Bullitt[22] described a method for eliminating pseudo-agglutination in typing and cross-matching of blood, following gelatin infusions.

The clinical studies on intravenous gelatin[6,7,12,16,21,23-25,32,37,39-41,44], like the experimental work, have been directed largely toward the treatment of shock from hemorrhage, trauma, and burns[6,16,25,37]; gelatin infusions have been consistently endorsed as a substitute for plasma for emergency use in these conditions. Considerable interest has been shown also in the possible use of intravenous gelatin solutions as supportive treatment in debilitated and undernourished patients being subjected to surgical or medical treatment[12,21,23,24,32,39,41,44]. The consensus is that gelatin solutions have some value in these conditions, but the results reported are not entirely consistent.

The laboratory studies on the effect on the blood proteins are somewhat at variance in the published reports. Some patients apparently show a positive nitrogen balance when gelatin is administered intravenously as a nutritional source, and others do not. The effect on the serum proteins is not entirely clear, though it seems quite generally accepted that there is a decrease in the concentration after the administration of gelatin. This effect was not observed in our laboratory studies. The immediate increase in blood volume after gelatin injections has been noted in all the experimental and clinical studies, with a corresponding decrease in the hematocrit. The evidence regarding the retention of gelatin, as indicated by the excretion in the urine, is most confusing. The amounts excreted during the first 48 hours seem to vary from 25 to 80%. As already mentioned, the retention of gelatin in the body evidently is influenced by the molecular weight of the gelatin, the concentration of the solution, and the metabolic and clinical condition of the individual to whom it is administered.

The diuretic effect of gelatin solutions has not received much attention in the literature, although the results in a few cases reported by Koop and his co-workers[21,23] and in the series reported here suggest that such preparations may have some clinical value for this purpose, especially in cases of nephrotic edema. An experimental study on normal dogs reported by Bridger *et al.*[2] also called attention to the diuretic effect of a 6% solution of gelatin. These findings would seem to indicate that additional studies along this line, with careful selection of cases, might prove fruitful from a clinical standpoint. The relationship of the type and concentration of the gelatin used to the amount retained by the body, and also the relationship of these factors to the diuretic effect in cases of edema of various types, need to be further investigated. It is almost impossible at present to compare the results reported by different workers, because of the lack of standardization or uniformity in the preparations and concentrations used in different investigations, both experimental and clinical.

Summary and Conclusions. Twenty-four patients with non-surgical conditions, more than half of them with evidence of liver damage, received a single injection of 500 cc. of a 10% solution of gelatin intravenously. One patient (Case 24) also received 4 subsequent infusions of the same amount. Detailed laboratory studies, including total proteins, nonprotein nitrogen, urea clearance, hemoglobin, hematocrit, urine volume, blood volume, bromsulphalein retention and cephalin-cholesterol flocculation tests, were performed before and after the injections of gelatin. The gelatin in the blood and urine was also determined at intervals over a 48-hour period.

The findings showed no significant changes following the administration of 50 gm. of gelatin in a 10% solution, except for an immediate increase in blood volume and a decrease in the hematocrit, and an increase in urine volume 24 to 48 hours after the injection. The increase in urinary output was greatest in patients with edema of renal origin and less striking in those with ascites owing to liver disease. Approximately 25 to 30% of the gelatin administered was excreted in the urine during the first 24 hours. Excepting in 3 patients with nephrotic edema, no appreciable quantity of gelatin was found in the urine at the end of 48 hours, and only minute amounts remained in the plasma.

The principal positive conclusion to be drawn from this investigation is that it indicates the need for additional stud-

ies as to the metabolism of gelatin in patients with various clinical conditions. Administration of gelatin solution to patients with nephrosis would seem to offer a worthwhile field for special study, with additional experimentation on optimal methods to be used in such treatment.

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THE FALLOPIAN TUBES

BY FRANK B. BLOCK, M.D.

Gonorrhea. The introduction of antibiotics into gynecological therapy has considerably affected the incidence and importance of inflammations of the Fallopian tubes. Not many years ago the literature was replete with articles dealing with such topics as the proper timing of operations for tubal inflammations and as to how radical such operations should be. These papers dealt, of course, with the management of advanced inflammatory disease which was one of the most common ailments in gynecological practice. The use of heat has always been advocated as a treatment in such cases, at first, merely in the form of hot douches. Later various mechanical gadgets were invented to keep constant prolonged heat in the pelvis, either by means of circulating hot water or by various electrical modalities. With the introduction of the sulfa drugs, gonorrhea was controlled better than by any previous therapy and, in turn, the antibiotics have largely superseded chemotherapy. The result has been that by quickly curing lower genital infections, inflammatory diseases of the tubes have become relatively rare and may soon join such museum pieces as empyemas and mastoid infections.

INCIDENCE. This does not mean that gonorrhea has disappeared; indeed, Peters[19] states that it is still the most prevalent communicable disease in this country. Her opinion is based on studies made upon 2,832 patients in a gynecological clinic of a Kaiser shipyard employing 23,000 women. She found that in 13.8% of all new gynecological cases bacteriologically proved gonorrheal infection was present. An analysis of their complaints shows that a large percentage of the patients presented symptoms which are not usually mentioned as, or suspected of, being characteristic of gonorrhea. Almost one-fourth of the patients presented themselves with menstrual difficulties, which could easily have led to the

wrong diagnosis if bacteriologic studies had not been made. Since irregular bleeding and prolonged bleeding are often the only indication of the infectious process, it is possible that some changes occur in the endometrium. The most frequent symptom complained of was abdominal pain, but menstrual disturbances took precedence over the most widely quoted triad of symptoms: urinary frequency and urgency and vaginal discharge. She believes that it is important to make bacteriological studies of women even in the presence of bleeding, in order to prevent the tragedies of chronic gonorrhea.

DIAGNOSIS. King[14] emphasizes that the responsibility of making a diagnosis of gonorrhea or ruling it out in an adult female is a serious one for any doctor, because of the social, legal, and public health aspects. He has studied over 6,100 smears and 3,200 cultures in the diagnosis of 598 cases. A single smear missed 59% and a single culture 38% of the infected cases, but 3 smears and 3 cultures missed only 0.2%. The culture proved 1.7 times as accurate as the smear for diagnosis, but no more accurate than the smear for the detection of treatment failures. Therefore in making this important diagnosis, he proposes that in order to rule out gonorrhea a minimum of 3 smears and 3 cultures, all negative, should be obtained, while to determine a cure, a succession of smears and cultures over a period of 2 months should all be negative.

TREATMENT. Although antibiotics are the preferred agents for treatment at the present time, it might be of passing interest to recall the great improvement in therapy which the SULFA DRUGS achieved. Whereas formerly gonorrhea was treated largely by local applications for long periods with doubtful results, Strauss and Grunstein[25] reported a great saving in time and effort by the use of sulfathiazole. Their series of 615 women consisted of prostitutes under arrest during war time. With a 10-day course of medication without local treatment the results were remarkable for those times. Of the 488 patients who completed treatment and were discharged after 4 consecutive negative smears and 3 negative cultures, 441 (90.4%) were negative after the first course of sulfathiazole and 47 were failures, of which 42 became negative after the second course of treatment, raising the cures to 98.9%.

With the advent of PENICILLIN, and particularly since its cost has become negligible, chemotherapy has largely been discarded. It should be remembered that in some advanced cases of pelvic inflammation it may be difficult to determine the etiological agent, whether gonococcal, streptococcal or colon organisms. In such cases penicillin may be ineffectual, and the report of Stevenson, Kohlerman, Snider, and Schlingman[24] on the use of chloramphenicol is worth noting. They have treated pelvic inflammatory disease with sulfadiazine, penicillin, and streptomycin, either alone or in combination, with satisfactory results for the most part, but there was a certain number of cases which responded poorly or not at all. Of 21 patients receiving this preliminary antibiotic therapy, there was no response in 16 cases, the response was poor in 3, and the response was good in 2, whereas only 3 patients failed to respond adequately to chloramphenicol therapy. The failure was due in 2 cases to the fact that the pathogenic bacteria were outside the antibiotic spectrum of chloramphenicol, and in the third patient to inability to administer the agent effectively. The bacteria usually present, often mixed, were *Escherichia*

coli, nonhemolytic streptococci, and *Aerobacter aerogenes.* Thus it may be seen that although the gonococcus may be the original infecting organism, various organisms may be present when pelvic inflammatory disease is well established. The clinical response to CHLORAMPHENICOL therapy consisted in marked symptomatic improvement, usually within 48 hours, rapid disappearance of the peritonitis, and subsequent anatomic regression of the tubo-ovarian inflammatory masses, the patients being ready for the exploratory laparotomy within 3 to 4 weeks on the average. Women who had large pelvic abscesses were treated so effectively with chloramphenicol that posterior colpotomy, with drainage of the abscess, was not necessary.

The SURGICAL TREATMENT OF SALPINGITIS has assumed a secondary position. As previously stated, the curability of lower genital infection has greatly decreased the number of cases which progress to the salpingitis stage, and of those that do, relatively few will require operation. In an effort to conserve as much tissue as possible when operation is necessary, Falk and Weitzner[8] over 10 years ago stated that practically every case of primary gonorrheal infection of the tube can be cured if re-infection can be prevented. As a result of their studies they reached 5 conclusions: 1) that when a patient had a complete occlusion at the uterine end of the tube, tubal infection did not recur and pus did not collect in the tubes; 2) that the uterus was the necessary avenue through which the infection reached the tubes from the cervix and external genitalia; 3) that even in the presence of the uterus, a total absence of infection from the internal os downward prevented re-infection; 4) that the tube cured of infection did not re-infect itself, 5) that salpingitis did not develop in those patients in whom the connection between the uterine cavity and the tubes had been broken, in spite of a gonorrheal infection of the lower genitals. Based on these findings they suggested that resection of the tubes at the uterine ends carries a minimum surgical risk, and that if it will clear the condition and prevent re-infection, it should be the method of choice. They stated that tubal resection is indicated in those patients who have had repeated attacks of salpingitis covering a period of 1 year with a relative disability during this time. They should give a history of sterility during this period and on vaginal examination should show persistent palpable masses. After the abdomen is opened the condition of the ovaries is the deciding factor as to the type of operation to be performed. If an ovarian abscess or cyst is found, the tube and ovary are removed; but if no ovarian lesion is found, resection of the tube may be done, leaving the ovary alone.

A recent evaluation of Falk's procedure has been presented by Freed and Kimbrough[9] based on 62 cases with clinical relief in 95%. Three patients later developed severe gonorrhea of the lower genital tract but none of these developed any evidence of salpingitis and no subsequent operative procedures were necessary in any case. They consider the procedure simple and safe and have found that the generous use of antibiotics will decrease the preoperative hospitalization. The technique of the operation as originally described by Falk is quite simple. A figure-of-eight stitch is inserted in the uterine horn, proximal to a hemostat placed on the uterine end of the tube. A V-shaped excision of the uterine end of the tube is carefully made so as not to injure the underlying ovarian branch of the uter-

ine artery. The proximal end of the tube is then freed from its mesosalpinx by cutting the mesosalpinx close to the tube for a distance of about 1 cm. The figure-of-eight suture is then tied and a ligature is applied to the cut end of the tube and the hemostat removed. The long end of this suture is threaded on a needle which is passed through the posterior wall of the uterus below the round ligament of the ovary and tied. This automatically causes the cut end of the tube to be inverted under the tube itself. The same procedure under the same conditions is carried out on the other side.

Tuberculosis. In reviewing the course and treatment of genital tuberculosis at the University of Freiburg, Keller[13] states that this disease has always been an important one since the first monograph on the subject was published there by Hegar in 1886. The disease is a secondary one and occurs most frequently after pulmonary tuberculosis. The route of extension may be hematogenous, lymphogenous, or by direct continuity. The hematogenous route is the commonest method of origin, while the lymph route is rare. Although primary tuberculosis of the genital organs is a possibility, it is extremely rare and then oftenest involves the external genitalia. The usual site of the disease is in the tube and the patients are mostly between 20 and 30 years of age.

Diagnosis. The diagnosis cannot be based on any specific symptom. The patients complain of a drawing and sticking pain in the lower abdomen, but the amount of pain has no relationship to the size of the mass, since often a large mass will cause very little discomfort. Two-thirds of the cases have no menstrual symptoms, because the ovary itself is seldom the site of the disease. The general physical condition in most cases is only slightly disturbed. The tuberculin test is of little value in the diagnosis. The history is often of much value, since two-thirds of the patients have a history of tuberculosis themselves or in their family and a similar number show a tuberculous lesion elsewhere in the body. Three-fourths of the patients are sterile. In many cases the diagnosis can only be made at operation or by histological examination of the removed specimen.

Prognosis. The prognosis depends on the extent of the disease. In one type the disease is well localized and runs a chronic course with a low-grade fever and few symptoms and the prognosis is good. In the other type, however, there is a stormy course with septic temperature and marked effect on the general health with a bad prognosis. If there is advanced tuberculosis in other organs, the prognosis depends on that of the primary focus.

Treatment. The treatment recommended is exploratory laparotomy in all suspicious cases. If ascites is present, it is drained. If the adhesions are not too dense, the involved organs, usually the tubes, are removed. The ovaries are seldom removed, as they are rarely involved. Roentgen therapy may be given either after operation or as a primary treatment, and the dosage should be small, since a castration dose is necessary only in the few cases in which there is extensive hemorrhage. In some cases only conservative measures to build up the general health may be used. In this series, 19 patients were operated upon with 15 cures, 10 patients were treated only with Roentgen therapy with only 3 cures, while among 9 patients treated by general conservative measures there were no cures.

Goodall[10a] agrees that pelvic tuberculosis is essentially a descending disease and states that not a single undoubted case of ascending infection has

ever been presented. Even in women married to men with genital tuberculosis, implantation of the disease through intercourse has never been proved. When the tubercle bacilli have reached the peritoneal cavity, one of 3 conditions may develop: 1) general tubercular peritonitis, 2) slight cryptic local pelvic tuberculosis, or 3) non-reactive invasion of the peritoneal cavity. In the diffuse tuberculous peritonitis, the tubercles are usually most abundant in the pelvic region, and become more sparsely scattered as one ascends in the peritoneal cavity. This peritonitis may be dry or moist. In the dry type there may be no appreciable abdominal cavity because the surfaces of the various organs are joined by a buttery exudate.

Goodall is of the opinion that this type of peritonitis practically always heals spontaneously and that the abdomen should be closed as soon as the diagnosis is made. While it is not easy to make the diagnosis before operation, the history of a previous attack of peritonitis, whether confirmed as tuberculous or not, should be given due consideration. If the patient is a virgin, other septic processes are practically ruled out, but endometriosis cannot be excluded. The history of a recent abortion almost rules out tuberculosis and endometriosis, and the presumption would be that the pelvic process is a septic one. He believes that surgical treatment of pelvic tuberculosis is rarely justifiable if the diagnosis is certain. Exploratory operation is merely a diagnostic procedure, and manipulation should cease as soon as the diagnosis has been confirmed. He emphasizes that 3 diseases produce adhesions which are in a class by themselves: namely, tuberculosis, malignancy, and endometriosis. In all other types of adhesions the lines of cleavage are readily found, and one can outline each organ by blunt hand dissection, but not in these 3 diseases, in which the lines of cleavage disappear and juxtaposed organs become inseparably fused. If one persists in separating such structures, especially if intestines are involved, fistulae readily develop. Prior to operation a clinical diagnostic aid may be the use of local heat to the pelvis; this usually helps chronic inflammatory disease but nearly always renders a tuberculous patient more uncomfortable. He has never regretted a conservative diagnostic operation, but surgical enucleation has given him many sad exeriences.

A statistical study of this disease has been made by Auerbach[2], who reports that in 571 consecutive autopsies in females having tuberculosis, 52 showed tuberculosis of the genital organs. The tubes were involved 49 times, the uterus 29 times, the ovaries 15 times, and the vagina twice. The involvement of the tubes was bilateral in 46 cases, the abdominal ends being first and most extensively involved. In all cases the infection was hematogenous, usually from the lungs. In the early stages of the disease the size, shape, and form of the tubes were not altered, but as the process progressed, the tubes became thicker and softer and on cross section were almost entirely caseous. The process begins with the development of foci in the wall of the tube, which perforates into the lumen and spreads to the remainder of the tube. Auerbach emphasizes that primary tuberculosis was not present in any of his cases and he doubts its occurrence.

The employment of irradiation therapy by means of Roentgen-rays in this disease is discussed by Campbell[4], who states that the production of a temporary or permanent castration conserves the patient's blood and raises her resistance, which may be important to

the anemic patient, especially since tuberculous women are often unfavorably affected by their menses. The dosage which he has used is not large enough to affect the white blood cells. He states that it is a well known fact that Roentgen rays do stimulate the production of young fibroblasts, so important in the conversion of tubercles into fibrous tissue. The rays are also useful in reducing secondary inflammation and infection, and this is important in the healing of a tuberculous process. In his work he has found no evidence that fistulae, dissemination of the tuberculous process, intestinal obstruction, and perforation of a viscus are serious complications of Roentgen ray therapy. On the contrary, excellent results were obtained; but the treatment should never be given unless the diagnosis has been definitely established, usually by some exploratory procedure.

Since streptomycin has been found of value in the treatment of some forms of tuberculosis, it is logical that it should be tried in gynecological tuberculosis. Sered, Falls and Zummo[22] report 16 patients with genitoperitoneal tuberculosis who were subjected to streptomycin therapy for 6 to 8 weeks, then operated upon and given another 3-week course of the drug. While one patient was receiving 2 gm. of streptomycin daily, vestibular symptoms developed which subsided with the reduction of the dose to 1 gm. per day. All subsequent patients were given the same dosage in the form of 0.5 gm. twice daily. During the preoperative period of clinical observation, while receiving streptomycin, all patients showed some improvement and the technical difficulties at operation were less formidable. The only complication was in 1 patient who became streptomycin-fast and subsequently died, having developed a spontaneous ileostomy 2 weeks before her death. They consider streptomycin a valuable adjunct in the treatment of this disease.

Actinomycosis. In a report from the Mayo Clinic, Paalman, Dockerty, and Mussey[18] state that actinomycosis of the tubes is one of the less common diseases of these organs, and in the past the outcome of such involvement has not been encouraging. However, the advent of chemotherapy has markedly changed the prognosis. The causative organism is a delicate, thermolabile, anerobic fungus named *Actinomyces bovis*, and there are 2 views as to its mode of entry into the body. Supporters of the exogenous route cite cases giving a history of chewing raw grain or grass and cases in which barbs of grain have been found in the lesions. The bulk of evidence supports the endogenous route, since Actinomyces are normal inhabitants of the mouth and intestinal tract. In the pelvis the disease is usually restricted to the tubes and ovaries. The well known resistance of the pelvic peritoneum and the tendency toward localization of infections in this area may account for the early seemingly benign course and protracted illness without more frequent evidence of early generalized peritonitis.

As a rule, a granulomatous tuboovarian mass is seen adherent to surrounding structures, varying in size from a walnut to tumors filling the entire lower abdomen. Such masses are greenish white or yellow, soft, friable, fluctuant and elastic, but occasionally may be hard. The surface may be smooth or roughened, most often has a moth-eaten appearance and pus may exude from the tumor. On cross section cavities of various sizes and shapes are seen; these are filled with pus of varying color in a meshed network of milky-white to grayish-black

connective tissue. The disease spreads by direct extension or by way of the blood stream, rarely by the lymphatic route. Usually the lesions progress peripherally, producing adhesions to, and abscesses of, contiguous structures, which eventually rupture spontaneously to the surface with the production of sinuses. The organism is capable of invading bone as well as soft tissue.

The early symptoms and course of this disease simulate pelvic inflammatory disease of other types, and when more acute, may resemble appendicitis. The diagnosis is usually made by microscopic study of the material removed at operation or by culture. The early symptoms of pelvic pain, vomiting and fever, and the presence of a mass in the abdomen or pelvis do not lead to a positive diagnosis, since these signs are more often associated with pelvic inflammatory disease of other causation. The possibility of actinomycosis should be kept in mind when medical treatment fails, especially if the sedimentation rate remains high. Microscopically the colonies are difficult to find, and repeated sections should be made when the lesion is granulomatous and on section reveals multiple abscesses.

The treatment of this disease is both medical and surgical, with radical removal of all diseased tissue as the ideal. Although iodides and Roentgen ray therapy still are of value, the use of sulfonamides and penicillin in large doses for long periods gives the best results. In spite of radical surgical treatment and chemotherapy, the prognosis still must be regarded as serious.

Salpingitis Isthmica Nodosa. An interesting pathological condition which was described about 60 years ago under the above title is one in which thickened areas appear in the tubes, chiefly in the isthmic portions. For many years these nodules were thought to be of an inflammatory nature, consisting of nests of glandular tissue, sometimes connected with the lumen

Schenken and Burns[21] have made a study and classification of such lesions and suggest that the nests of epithelium which appear to be inclusions are, in reality, diverticula. Their study was based upon 329 nodules in the walls of Fallopian tubes of 208 patients, in which 81.7% of the nodules were due to diverticula of tubal epithelium alone or in association with acute or chronic inflammatory lesions. In 11.2% of the nodules there were inflammatory lesions without diverticulosis; 6.7% were due to endometriosis, and 0.3% were due to metastatic carcinoma of the endometrium.

The pathogenesis of the most common lesion, diverticulosis, is of great interest, since the frequent association of inflammatory processes with the diverticula suggests that inflammation is an etiologically related lesion. This view is supported by other workers who have described epithelialization of the cavities of abscesses which have ruptured into the lumen of the tube. It is also possible that deep ulcers of the mucosal surface may allow the epithelium to gain access to the muscular coat. From an anatomic standpoint the absence of a muscularis mucosae in the tube makes the muscular coat more accessible to invasion by the tubal epithelium. Once the epithelium is established in the muscular coat, whatever the means of invasion may be, it apparently proliferates slowly and invades the muscular tissue widely. In addition, muscular contractions of the tube may tend to push the acini between the muscle fibres, and it is also possible that cyclic hormonal influences may cause proliferation of the epithelium.

Carcinoma. Primary carcinoma of the Fallopian tube is a rare condition.

accounting for only 1 out of every 625 carcinomas of the female genital tract in the experience of Lofgren and Dockerty[10] of the Mayo Clinic. They state that for the most part it is a disease of the menopause and has not been reported in prepuberal years. Symptoms are insidious in onset with vaginal discharge, pelvic pain, and abdominal tumor as cardinal symptoms, which, however, rarely lead to a correct preoperative diagnosis. The evolution of the disease is more rapid than is indicated by its symptomatology, and the majority of patients demonstrate lesions of doubtful resectability at the time of operation. The appearance of the lesion is sometimes deceiving, since it may mimic closely familiar tubal conditions of an inflammatory nature; therefore every distended tube should be opened before it is removed from the operating room.

Whenever carcinoma is found, regardless of any degree of apparent encapsulation, it should be treated by total abdominal hysterectomy with bilateral salpingo-oophorectomy, in addition to removal of any discernibly involved regional lymphatic nodes and peritoneal implants, and postoperative Roentgen therapy should be given. In spite of these measures the number of 5-year cures is disappointingly small. They state that pathologists who are unfamiliar with the condition will often have difficulty in establishing the primary nature of the lesion and should remember that the tubes are frequently involved in metastasis from ovarian and uterine sources.

While the foregoing report is that of pathologists, it should be correlated with that of clinicians Judd and Masson[12] of the same clinic. They agree that because of the rarity of the condition and the lack of a clear-cut clinical picture, the diagnosis is seldom made before operation, but certain symptoms and signs may lead to correct diagnosis if they are properly evaluated. They believe that the most common symptom of primary carcinoma of the tubes is leukorrhea, which may be serous or serosanguineous, and usually has an offensive odor. If curettage is performed, the endometrium usually is found to be normal or atrophic, for the malignant lesion rarely spreads to the endometrium. Pain in the lower portion of the abdomen or pelvis is another symptom frequently encountered, usually appearing much earlier in this condition than in other malignant lesions in this region. The pain is usually not severe, but there may be an intermittent cramplike pain. Periods of relief are associated with a gushing vaginal flow, the so-called "hydrops tubae profluens". It is believed that the pain is associated with distention of and accumulation in the tube, and when the discharge is expressed from the tube, relief is obtained. Irregularity of the menstrual cycle completes the triad of symptoms most commonly encountered in this disease. Metrorrhagia is the most common menstrual variant, but since this disease occurs in the menopausal age group, the significance of this abnormal bleeding may not be fully evaluated. The significant finding on pelvic examination is a tumor in the adnexal region which can be palpated in nearly 80% of the cases.

At the Free Hospital for Women in Boston the incidence of primary tubal cancer is nearly twice as great as at the Mayo Clinic according to Hu, Taymor, and Hertig[11], who report on 12 cases out of 3,878 primary malignant lesions of the female genital tract. Sterility was associated in 27% of the cases, but vaginal discharge was the most common symptom. Other common signs and symptoms were pain, tumor mass, menstrual inrregularities,

or postmenopausal bleeding, but they did not find that "hydrops tubal profluens" was a characteristic symptom. They believe there is a fairly consistent correlation between histological grading and prognosis, the well differentiated papillary forms having a good prognosis, although the 5-year survival of the entire series was 40%. They also believe that radical hysterectomy followed by irradiation is the treatment of choice.

Tubal Patency Tests. For many years the patency of the tubes has been tested by either the use of a gaseous or liquid medium, and undoubtedly much valuable information has been obtained in this manner. In evaluating such tests Miller[17] warns of some of the dangers and mentions the contraindications to the performance of these diagnostic procedures.

The most important contraindication is the presence of genital tract infection. He states that most morbidity following tube testing results from failure to recognize cervicitis or incompletely subsided salpingitis. Since satisfactory evaluation of genital infection is not always possible at the initial visit, it is seldom wise to perform the test at that time. Pregnancy is an obvious contraindication; therefore knowledge of the menstrual history and repeated pelvic examination just before the test is important.

While air has been extensively used as a testing medium, it should never be used since most of the deaths which have been reported following insufflation were the result of air embolism. The test may be done at any time during the menstrual cycle, but most investigators prefer the week after menstruation. Uterotubal insufflation, using gas, and uterosalpingography, using liquid, have been looked upon as competitive procedures, whereas they should be considered as complementary, one supplementing the other. He believes that insufflation should be the initial test and that it will give all the information needed in the majority of cases.

Uterosalpingography. For doubtful cases and those presenting definite evidence of nonpatency, he prefers uterosalpingography with its visual proof of tube status and better evaluation when salpingostomy is to be done. Such operation, however, should not be done until several checks for tubal patency have been made, since spontaneous restoration of tubal continuity occasionally occurs. Both types of tests have a therapeutic as well as a diagnostic value, since pregnancy often occurs within a month or two after the test, probably due to the removal of a mucous plug or the disruption of adhesions which may have been sufficient to interfere with the migration of the ovum.

In the performance of hysterosalpingography, both aqueous and oily media have been used and each type has certain advantages and disadvantages. A comparative study of the various media in 200 subjects has been reported by Brown, Jennings, and Bradbury[3], who found that the absorption of radiopaque material from the peritoneal cavity after such tests varied from 25 to 45 minutes with aqueous media, to 3 to 6 months with the iodized oils. They summarize their study by stating that iodized oils have the advantage of giving dense shadows and longer duration (several hours or days after injection), during which time Roentgen-ray films can be taken, but they have the disadvantages of retention of the oil for months, transient acute peritoneal reaction, and the development of oil retention cysts with foreign-body granulomas and oil emboli. On the other hand, aqueous media have the advantages of rapid absorp-

tion and renal excretion, easy physical handling, elimination of retention cysts and emboli, and of giving satisfactory shadows. However, aqueous media have certain limitations due to the rapidity of absorption, which require films to be taken within 10 minutes after injection, and the low viscosity, permitting too rapid peritoneal spill, overshadowing the tubal outlines. On the whole, they have found the aqueous agents to be preferable.

DECKER TEST. A simple technique to test tubal patency has been described by Decker[6] which takes advantage of the negative intraperitoneal pressure when the patient is in the knee-chest position. After the patient is placed in such position, the perineum is elevated with a Sims speculum. The cervix is grasped with a tenaculum and painted with an antiseptic, and a cannula or catheter is introduced into the uterus. Because of the negative intra-abdominal pressure, an immediate pneumoperitoneum results if the tubes are patent. The amount of air entering the abdomen is usually about 150 to 300 cc. as demonstrated by Roentgen ray. The characteristic shoulder pain occurs on resumption of the sitting or standing position. He believes that this method has several advantages; very few instruments are needed, the air enters the abdomen only if the tubes are patent, not spastic, and as a result of negative pressure created beyond the distal end of the oviduct. The pressure within the uterus and tube is never elevated and the danger of air embolism is reduced as are other accidents that result from high intrauterine or intratubal pressure. When a pneumoperitoneum results following this procedure, at least one tube may be considered patulous.

SPECK TEST. Another new test for patency which has been described by Speck[23] is based on the premise that phenolsulfonphthalein is not easily absorbed (if at all) from the normal vaginal mucosa, endocervix, endometrium or endosalpinx, but is readily absorbed from the peritoneal cavity. Thus, if the tubes are patent, dye injected into the uterus will pass into the peritoneal cavity where it will be absorbed, carried to the kidneys, and excreted in the urine, which will turn pink or red when alkalinized. If the tubes are closed, this will not occur, and the urine will not give a positive test. In performing the test, a cannula is placed in the uterine canal, as in the Rubin test, and 6 mg. of phenolsulfonphthalein, diluted to 10 cc. with isotonic sodium chloride solution, are injected slowly into the uterine cavity. If the tubes are closed, or if there is tubal spasm, there will be some resistance to the flow and the patient will complain of cramps, but if the tubes are patent and the injection is slow, there will be little resistance or discomfort. If there is any leakage around the obturator, it will be readily visible and will not interfere with the accuracy of the test. The cannula is removed at the end of 10 minutes. A tampon is placed in the vagina, the speculum and tenaculum are removed, and the bladder is catheterized. The urine is collected in a test tube to which a few drops of 10% sodium hydroxide solution are added. If the urine turns pink or red, the tubes are considered patent. If the urine remains clear, the patient is given a glass of water and 20 minutes later is recatheterized. If the urine still remains clear after the addition of the sodium hydroxide solution, the tubes are considered closed.

RUBIN TEST. In the performance of the Rubin test to determine the patency of the tubes, the average case requires a pressure of 120 mm. of mercury to open the tubes and then the

pressure falls to 80 mm. For those who are not too familiar with variants in this procedure, it is well to remember the warning given some years ago by Goodall[10b] that in some cases there is a preternaturally large lumen and in such cases an initial pressure of only 40 mm. of mercury is required to open the tube, after which the pressure falls to about 20 mm. He believed that this excessive permeability has a direct clinical significance in exposing the pelvic cavity to either chemical or bacterial invasion, and reported 4 cases of chemical peritonitis following vaginal douches, in 3 of which a bulb syringe was used, while in the fourth a fountain syringe was used. He tested 2 of these patients and found that the tubes were patulous to 50 mm. in one case and 40 mm. in the other. He had also seen several cases of pelvic infections in virgins in whom the tubes were abnormally patulous.

Tubal Sterilization. There is an old saying among gynecologists that there are two conditions for which a woman would sell her soul; one is to become pregnant and the other is not to become pregnant. Just as it is difficult to assure any given woman that she will become pregnant, it is also impossible to be certain that pregnancy will not occur in spite of any operative procedure that may be done, except of course, removal of the uterus and both ovaries. When it is desired to sterilize a woman, it is customary to perform some obstructing type of operation upon the tubes so that the ovum cannot be fertilized. Nature does not always agree with the ideas of the surgeon, and there have been failures after every type of the dozens of procedures which have been advocated. Connors, Cresci, and Glass[5] have reported an almost incredible case of a vaginal delivery of a 6-months living child 4 years after a supravaginal hysterectomy. Such a pregnancy must depend upon the formation of a fistulous tract between the vagina and the ovary. In performing a subtotal hysterectomy, it is common practise to attach the remaining adnexa to the cervical stump; thus the proximal end of the tube is adjacent to the cervical canal.

Temporary Sterilization. There may be cases in which it is desirable to produce temporary sterilization, with the idea that fertility could be restored, should conditions warrant it. The operation described by Aldridge[1] in which the outer ends of the tubes are buried in peritoneal pockets would be of value in such cases. Temporary sterilization might be recommended for a woman who, for reasons of her own, refuses permanent sterilization or who suffers from a chronic disease, such as tuberculosis, which contraindicates pregnancy, but which might improve sufficiently at some future time to permit pregnancy. Usually, however, sterilization is intended to be permanent and a tubal ligation is performed.

Tubal Ligation. There are 2 main types of tubal ligation which vary in minor details. The Madlener operation consists of crushing a loop of the middle portion of the tube and then ligating the crushed portion with a nonabsorbable ligature. The Pomeroy procedure differs from this in that the loop of tube is not crushed but merely ligated with absorbable ligature material, and the portion beyond the ligature is excised.

Reporting on 233 sterilizations performed at the Sloane Hospital for Women, New York, Knight[15] states that after trying the Madlener and Pomeroy operations as well as cornual excision and segmental resection of the tubes, he found that the Pomeroy operation is a safe, simple, sure, and rapid procedure with 50% fewer fail-

ures than the Madlener operation, the latter being prone to the formation of a fistulous communication between the the ends of the tube as a result of the cutting through of the nonabsorbable ligature.

In a series of 101 cases sterilized by the Madlener operation at Johns Hopkins Hospital, there were 5 failures, according to Dippel[7], and of special interest is the fact that the areas of attempted sterilization were recovered at the time of a second sterilizing operation from both tubes of 4 patients and from 1 tube in the other. Each area was serially sectioned to ascertain the reason for failure. One patient had a very early pregnancy at the time of the Madlener sterilization. In 2 instances considerable regeneration of the tubal lumen occurred, so that the ligating suture must have been improperly tied or placed or slipped off the knuckle of tube. This error was bilateral in 1 case. In a fourth patient the tubal lumina were apparently completely obliterated, but eventually another lumen was reestablished on one side by endosalpingosis. In the fifth instance both tubal lumina were replaced by scar tissue but a small tuboperitoneal fistula developed as a result of endosalpingosis. He believes the failures could be reduced by more careful adherence to the original technique.

Madlener stated that a dull clamp with a broad crushing area (9 mm.) is the only safe instrument to employ. To avoid breaking through the serosa while crushing the loop to paper thinness, the clamp must be applied squarely to a loop which is freely movable, lateral to the midpoint of the tube and including a bit of mesosalpinx.

Restoration of Fertility. Some patients who have been sterilized by tubal ligation may desire to have their fertility reestablished but would not care to undergo another abdominal operation. It might be well to remember that the desired result has been accomplished in 5 cases by Rubin[20] by means of insufflation with carbon dioxide at pressures below 160 mm. of mercury. The more recent the ligation, the less pressure is required to open the tubes. Unless a portion of the tube has been resected, the artificially induced obstruction should yield to insufflation at a pressure of 200 mm. of mercury or less, but in experienced hands the pressure may be increased to 250 mm. The flow is regulated at the rate of 1 cc. per second or slower, the pressure rise and pain reaction being observed. About 100 cc. of gas is adequate and the procedure requires from 2 to 3 minutes at the first trial. If this fails, it can be repeated at suitable intervals. As to the manner in which insufflation opens the tubes, it has been noted that whether they have been previously crushed or not, the pathological change induced is localized at the point of ligation. A small fibrous band connects the severed ends of the tubal loop and the stricture is limited to a very thin segment of the endosalpinx and tubal serosa, in contrast to pathological strictures, which occupy more extensive portions of the lumen of the tube. As the tubes that have been ligated were normal previous to the sterilizing operation, they remain normal except at the point of ligation. This renders the surgical structure vulnerable to intratubal pressure.

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PHYSIOLOGY OF THE ADRENAL CORTEX IN INFANCY AND CHILDHOOD

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THE adrenal cortex of the human fetus is striking in its manner of development, differing from the common mode of organ growth in man. At birth, it is histologically unique, and undergoes rapid and profound changes in structure.

Available methods for evaluating adrenal cortical function indicate differences in the newborn infant and changes in the growing child, which are not entirely a function of body size. Physiologic variations in other organ systems of infants and the growing child can be interpreted in the light of the changing adrenal cortical state. Some such interpretations are speculative at the moment; others are founded on experimental and clinical observations. These individualities in the newborn and growing child warrant a correlation of early and recent data on the physiology of the adrenal cortex in early life.

The Fetal Cortex. The adrenal gland of the primate is one-third the size of the kidney, at birth. Within the first 2 weeks of postnatal life, this organ loses one half of its weight. The birth weight is regained by the 12th year of life, and reaches a maximum size at 40 years[20].

In a study of 2,768 cases, Scammon[36] described the growth of the adrenal glands in man, as rapid beginning at the 3rd fetal month, the weight reaching an average of 9.0 gm. at birth. They diminish in size at birth, due to the degeneration of a large portion of the cortex, and follow an irregular course of increment. At full maturity they are approximately double the neonatal weight.

Ekholm and Niemineva[13] found the ratio of adrenal to body size to be 1/213 at the 3rd fetal month, decreasing therafter to 1/394 at birth. Other endocrine glands are relatively smaller at the 3rd fetal month, and increase slowly until birth. In the adult, the ratio is 1/7000. It is believed "only natural that behind this phenomenon there must be function"[13] (this phenomenon of rapid pre-natal growth and early post-natal degeneration).

The adrenal cortex of the neonatal infant consists of 2 large zones[14,41]. A prominent hypertrophied "fetal cortex" lies between the true thin peripheral cortex and the medulla. The "fetal cortex" begins to degenerate immediately after birth and has completely disappeared by 1 year of age or earlier. It constitutes 85% of the

neonatal adrenal cortex, and with its involution the stroma becomes prominent. The "true" peripheral cortex of the newborn infant consists entirely of zona glomerulosa. The zona fasciculata appears in the 2nd post-natal week, and the zona reticularis in the 3rd month. The stroma of the "fetal cortex" is gradually compressed between the expanding latter zones and the adrenal medulla. Cytologic study[41] denies an earlier thesis, that the "fetal cortex" is the basis of the zona reticularis.

It is possible that the "fetal cortex" represents an early local response to maternal hormonal influences[31], which is supported by the involution of this region immediately after separation from the mother. This occurs rapidly in all newborn infants, whether premature or full-term. On the other hand, Wells[51] has presented evidence that the fetal hypophysis plays a role in the hypertrophy of the cortex. By decapitating (thus hypophysectomizing) fetal rats, *in utero*, it was shown that the adrenal cortex grew to only 60% of its size in control litter mates. The administration of adrenocorticotropin to decapitated fetuses produced marked hypertrophy of the adrenals. If a maternal influence is involved, one must assume that it operates via the fetal hypophysis.

A definite functional role cannot be assigned to this portion of the adrenal gland. Tobin[46] destroyed both adrenals of fetal rats on the 17th day of maternal pregnancy without impairing survival, normal body growth, and normal development of the other endocrine glands.

The relatively high excretion of 17-ketosteroids in the first few days of life, detailed below, has prompted proposals that the "fetal cortex" represents their origin. However, extracts of human fetal adrenals have failed to exhibit androgenic activity[31]. It is nonetheless possible that the precursors of these steroids are non-androgenic. Other evidence to be presented suggests a temporary hyperadrenal state during the first few days of life, but this is counterbalanced by indications to the contrary.

Adrenal Cortical Function. The status of adrenal cortical activity in infancy and childhood has been determined in 3 ways: 1) The various hormones or their metabolic products have been measured in the urine at various ages. The methods and the usual pediatric values have been discussed by the author elsewhere[1]. 2) Various systemic functions which are subject to the adrenal cortical hormones have been investigated as an index to the activity of the gland. 3) Finally, the ability of the adrenal cortex to respond to various stimuli has been examined.

Urinary Excretion of Steroids. Talbot *et al.*[42] have shown the excretion of 17-ketosteroids to be less than 1.0 mg. per day before 8 years of age. A rapid rise occurs at 8 to 12 years. Before the age of 8 years no further refinements according to age are normally possible because of the very low levels. At 12 years, at least 1.0 mg. per day should be excreted in the urine, rising gradually to adult levels which are higher in the male. This particular expression of adrenal cortical function therefore indicates a low level of activity until the onset of puberty. The rise at this time has been termed the "adrenarche". Otherwise normal children with earlier sexual development and body growth for their chronological age demonstrate larger quantities of this steroid in their urine at their age level[42], but do not exceed the normal limits for older children.

Available data reveal a relatively high urinary excretion of 17-ketosteroids during the first few days of post-

natal life. Read *et al.*[35] report a quantity generally exceeding 1.5 mg. at birth but falling within a few days to 0.5 mg. Day[8] records levels as high as 3.4 mg. per day in newborn infants, the largest quantities having been noted in infants born by Cesarean section. These findings are in agreement with those of others[34]. Four hypotheses are suggested as explanations for these elevated values shortly after birth. 1.) The hypertrophied "fetal cortex" may represent the source of these substances, although, as stated above, androgenic material has not been demonstrated in extracts of this tissue. It is possible that non-androgenic substances represent the precursors of these excretory products. On the other hand, the measurement of corticoids in the urine reveals a slight rise in excretion during the first few days of life, at the very time when the fetal cortex undergoes massive involution[35]. 2.) They may represent substances originating in the maternal adrenals and transmitted prior to birth, which are therefore excreted in larger quantity for a brief period thereafter. 3.) Adrenocorticotropic hormone from the maternal organism may stimulate the neo-natal glands with gradual subsidence of activity following separation from the prenatal source. This is discredited by data to be detailed later, which disclose a lesser response of the neonatal adrenal to exogenous adrenocorticotropin until after several days of its administration, when a more effective stimulation is apparent. This is presumably due to "priming" of the glands by the first doses; were the neonatal glands previously "primed" by the maternal hormone, the earliest response would be expected to be maximal. 4.) The stress of birth may stimulate the newborn adrenal via the pituitary–adrenal axis. Jailer[22] has shown that this axis may be relatively immature on the first day of life and incapable of response to stress. In addition, the excretion of corticoids (to be distinguished from 17-ketosteroids) is relatively lower during the first few days of life, although they ordinarily rise in response to stress.

The urinary corticoids, which are distinct from the 17-ketosteroids, may be determined chemically or biologically[1]. They probably arise from a different portion of the adrenal cortex and have different physiological activities. The corticoids include the "salt-water" and gluconeogenic hormones in this discussion.

Read *et al.*[35] have reported formaldehydogenic corticoids in the urines of 10 normal newborn infants, which ranged from 0.025 to 0.133 mg. per day. Venning[47] records similar values for the first few days of life. Corticoids, expressed as reducing substances, range from 0.26 to 0.62 mg. per day in the neonatal period. On the basis of body surface area, the excretion of corticoids is comparable to adult levels in infancy and childhood, with the exception of the first few days of life when they are slightly lower[8,28,33,43]. Thus the excretion of corticoids, when adjusted for body size, is constant throughout life, although the absolute quantities rise with increasing age.

Talbot *et al.*[43] have emphasized the constancy in the excretion of corticoids throughout life as related to body surface, whereas the 17-ketosteroids are held in abeyance until puberty (Fig. 1). This suggests an important alteration in adrenal cortical function at this time and is probably not due to a difference in the metabolism of these hormones, since administered testosterone proprionate causes an appropriate rise in 17-ketosteroids in children. Nor does Talbot[43] consider it likely that there is an altered response of the adrenal to endogenous adrenocorticotropin,

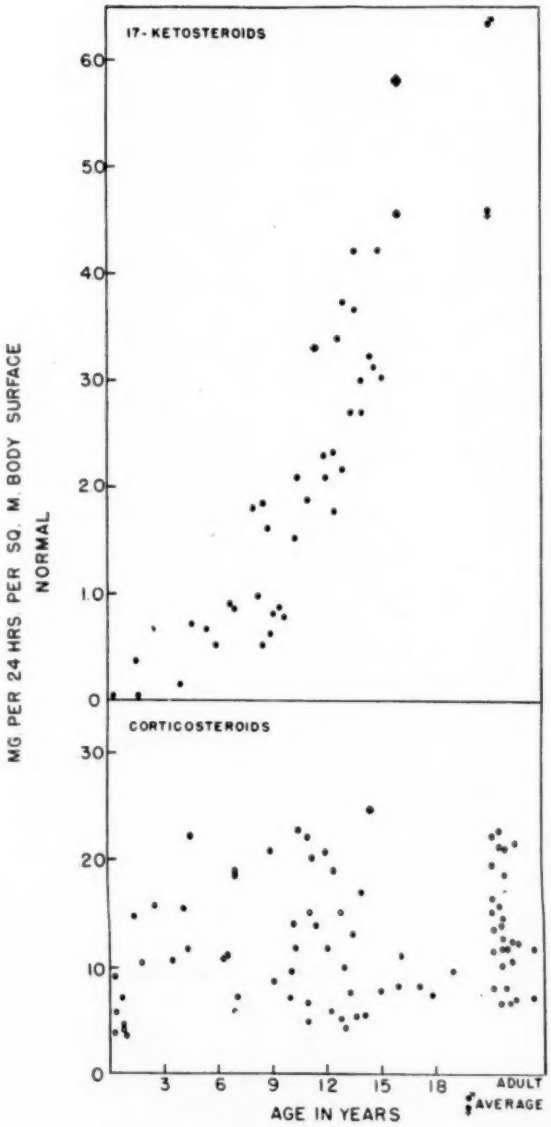

FIG. 1.—The urinary excretion of 17-ketosteroids and corticosteroids (copper reducing) at various ages, adjusted per square meter of body surface. The rise in 17-ketosteroids with increasing age and the contrasting stability of the corticosteroids is apparent. (Reproduced from "Proceedings of the 1st Clinical ACTH Conference," 1950, p. 33. Courtesy of Dr. N. B. Talbot[43], Boston, Mass., and the Blakiston Co., Philadelphia, Pa.)

since when administered in childhood it will produce rises in 17-ketosteroid excretion. He suggests that the human pituitary gland produces 2 types of adrenocorticotropin: one stimulating 11- 17-oxysteroids (corticoids), and the other, 17-ketosteroids. The former is secreted throughout life, and the latter manifests itself at the "adrenarche".

Venning *et al.*[50] have reported 4 to 17 gamma (average 11) of glucocorticoids per day in the urine of normal full-term and premature infants. Thus biologically active (glucogenic) corticoids occur in the urine at birth, although the zona fasciculata has not yet appeared in the adrenal cortex. These substances are probably not derived from the maternal organism, since the urine collections were not begun until the 3rd day of life. These levels represent about 1/4 to 1/6 the adult values of such material[47,48].

Hormones of the salt-water type (11-desoxy-) cannot be determined precisely by the present methods of chemical assay. Bioassay of urine may determine this type of activity, and the older methods are reviewed by Dorfman[10a]. Deming and Luetscher[9] have measured the degree of sodium retention in adrenalectomized rats produced by urine extracts of human subjects as a gauge of such hormones. This method has not proved entirely satisfactory in the author's experience[2]. Dorfman[10b,11] has applied a similar technique, by using radioactive sodium and potassium in rats, and this appears to have a high degree of sensitivity and accuracy. There are no data pertaining to infants with these methods.

Mineral Metabolism. Clinical measurements, based upon the observation of sodium, potassium, and water metabolism in the organism, have served as an indicator of desoxycorticosterone-like hormones. The low volume of urine in the first few days of life is well known. The average is 19 cc. on the first day, rising to 103 cc. on the third[44]. McCance and co-workers[29] have studied renal function in early life. Low chloride and sodium clearances in the newborn, related to a subnormal glomerular filtration with normal tubular reabsorption, have been described. The disproportion in these functions, with a relatively higher tubular activity, may be explained by the action of adrenal cortical hormones on the tubules. However, the potassium clearance is also low, and this is not consistent with the usual action of desoxycorticosterone. The anticipated "forced" excretion of chlorides in the urine of infants, in the presence of high plasma levels, did not occur[53]. In infants 5 weeks to 8 months of age, with plasma chloride levels of 400 mg. per 100 cc., the average urinary concentration was 314 mg., whereas 1.0 gm. would have been expected in the normal adult. These data are interpreted as signifying renal immaturity with limitations of excretion, as was borne out by lower urea and inulin clearances. Thus the low renal clearance of minerals in the infant cannot alone be considered a reflection of increased mineral–hormonal activity of the adrenal.

Smith *et al.*[37] have noted excessive urinary losses of sodium and chloride, with potassium retention, in edematous premature infants at the time that their edema subsides. It is suggested that these phenomena occur upon the withdrawal of desoxy-like hormones after birth, as the adrenal cortex undergoes rapid involution.

Klein[25] has shown that the kidneys of infants respond to the administration of exogenous desoxycorticosterone in a normal fashion, with sodium retention. Soffer *et al.*[38,39,40] had previously noted that, although desoxycorti-

costerone ordinarily produces renal retention of sodium, in the presence of a hyperfunctioning adrenal it leads to an increased excretion of sodium. Klein's studies may rule out the possibility of significant hyperfunction in infancy, in the light of Soffer's work. On the other hand, when adrencorticotropin was administered to 12 newborn infants[25], the excretion of sodium always rose after one day, often exceeding the dietary intake. This is a unique response, and it has been proposed that the immature adrenal may produce salt-excreting hormones under such stimulation.

Conn[4,5,6] has studied the relationship of the sodium concentration in perspiration to adrenal cortical function. It has been shown that there is a close correlation between the level of adrenal function (salt-water), determined by other methods, and the sodium in sweat. The sodium in the perspiration of 21 normal adults ranged from 15 to 60 mEq./L. (mean 42)[4]. In various hyperadrenal states, the levels were less than 15 mEq./L., while in Addison's disease they were generally above 80. Eisenmenger, Bongiovanni, Blondheim, and Kunkel[12] reported normal adult values as 12 to 95 (mean 60) mEq./L. Cooke, Pratt, and Darrow[7] reported an average sodium concentration of 4.8 mEq./L. (1.8 to 7.6) in infants from 5 to 16 months of age. This is far below the normal adult levels. In addition the sweat sodium in infancy did not lower in response to desoxycorticosterone acetate, as it does in adults, pointing to a possible maximal adrenal effect in infancy. The sodium–potassium ratio in the sweat of infants in an environment of 91° F. was usually less than 1.0, whereas in normal adults it ranges from 4.0 to 10.0. Eisenmenger *et al.*[12] showed that the saliva concentrations of adults were subject to the same adrenal influences as sweat. This was later reported by Frawley and Thorn[17] as well. In adults the range of sodium concentration in saliva was normally 13.1 to 41.0 mEq./L. (mean 22.6). The author's studies[30] in 6 normal and 5 convalescent children, aged 1 to 8 years, revealed concentrations of 4.1 to 9.8 (mean 6.0). If it is a valid assumption, that these differences between adult and child are due primarily to differences in activity of the salt-water hormones, then one may conclude that there is hyperaction of this phase of the adrenal hormones in infancy and childhood.

Bruch and McCune[3] were unable to demonstrate alterations in serum chemistry of early life which would suggest unusual adrenal cortical function. Miller[32] described a rise in the concentration of sodium in the serum after the first few days of life, which was thought to indicate a previous adrenocortical insufficiency. He also implied that such an insufficiency could account for the physiological weight loss in infancy, which he was able to limit by one-third, with the administration of desoxycorticosterone acetate. However, as described above[29,53], the limitations of mineral excretion in infancy may account for the rise in serum sodium, without any necessary relationship to the adrenal cortex. More recently Graham *et al.*[32] have noted normal or elevated concentrations of total base and chloride in the serum of newborn infants, although the plasma carbon dioxide was significantly lower than in adults. These findings do not conform to the expected diminution of sodium and chloride as in adrenal insufficiency. Jaudon[24a,b] has expressed a theory of physiologic adrenal hypofunction in early life, based on a group of debilitated infants responding well to a period of desoxycorticosterone therapy. Such infants were flaccid, tended toward de-

hydration, and often had diarrhea and emesis. Hemoconcentration occurred often with diminution of the plasma carbon dioxide, elevation of serum non-protein nitrogen, and a drop in serum sodium. The physiologic hypoglycemia of infancy was also invoked as an argument in favor of this thesis. Milder, transient degress of such adrenal insufficiency were thought to exist in infancy. No doubt these observations have led to an increased use of adrenocortical hormones in a number of nonspecific debilitating conditions in infancy.

Adrenal Cortical Stimulation. Forsham[16] and Thorn[45] *et al.* have shown that the integrity of the adrenal cortex may be tested by the administration of adrenocorticotropin. Following such direct stimulation of the adrenal cortex by this hormone, a diminution of circulating eosinophils of 50 to 80% normally occurs. In addition there is normally a rise in the uric acid:creatinine ratio and elevation of various of the adrenal steroids in the urine with continued administration. Epinephrin may be used instead of ACTH, but its mechanism of action is indirect. Presumably epinephrin stimulates the hypophysis which in turn produces endogenous ACTH. Thus the latter test depends upon the integrity of the entire pituitary–adrenal axis for a normal response. Various forms of stress are also known to produce adrenal cortical stimulation, via the pituitary–adrenal axis. Some studies have utilized these approaches to assess adrenocortical function in childhood.

Most of the available data concern the simplest test, namely, the response of circulating eosinophils to various stimuli. Lippman[27] reported the average eosinophil count as 370 per c.mm. on the first day of life, with a rise to 525 at 30 hours and 419 at 48 hours. Thereafter a diminution occurred. Read *et al.*[35] recorded the eosinophils as ranging from 469 to 969 per c.mm. in 4 newborn infants. Klein and Hanson[26] found an average of 359 ± 47 (range 78 to 988) circulating eosinophils per c.mm. in 30 newborn infants. On the second day, these were 420 ± 43; at 8 to 10 days, 268 ± 42. In general these counts exceed the adult range (60 to 200)[15] significantly, except for Jailer's data which reveal a mean of 187 (range 20 to 537) in normal full-term infants aged 1 to 7 days. It is tempting to propose diminished adrenocortical activity (11 and 17-oxyhormones) in the first few days of life, on the basis of these counts.

White and Sutton[52] believe that a diminution of 35% or more in circulating eosinophils should denote an adequate response in infants, and Jailer *et al.*[23] have found 40% an appropriate criterion of response. These are less than ordinarily anticipated in adults, but are based on numerous observations in early life.

Read *et al.*[35] report an adequate diminution of eosinophils in newborn infants, following administration of ACTH, even when there was insufficient effect to result in a rise of urinary steroids. Klein and Hanson[26] report an adequate diminution of eosinophils (37% fall or greater) after ACTH in only 9 of 73 infants under 7 days of age. Of 14 infants tested in the first 4 days of life, only 2 responded adequately; all but 2 of the same group responded on the same or smaller doses of ACTH (0.7 to 6.0 mg.) at the age of 7 to 15 days. Of 12 infants under 2 weeks of age admitted with various diseases, there was no significant deviation from the normal range of circulating eosinophils in 10, perhaps indicative of a failure of response to stress. Venning[47] has observed a more adequate response of the eosinophils on the 9th day of life than on the 2nd. Hain and Wilson[19]

report an adequate drop in circulating eosinophils with ACTH therapy in 23 children aged 6 to 13 years, and 6 of 8 older children responded well to stress (tonsillectomy and insulin).

The rise in the uric acid:creatinine ratio as a measure of response to ACTH is subject to limitations in younger age groups. In infancy there are wide daily variations in urinary creatinine, and the uric acid excretion is irregular, hence this index is of no value in very early life[35]. In older children[19] (6 to 13 years of age) the increase in this ratio following adequate ACTH stimulation is far smaller than in adults, ranging from −13 to 105%, with a mean value of +30 in normal and +4 in rheumatic individuals.

The response of the circulating eosinophils to epinephrin in infancy has been studied. As mentioned, the use of epinephrin involves an indirect circuit of adrenal stimulation. White and Sutton[52] report that 7 of 8 normal newborn infants showed an adequate diminution in eosinophils with epinephrin (0.1 to 0.15 cc. of 1:1000 solution). The majority of 12 premature infants weighing less than 2270 gm. responded poorly, with an average drop of 23%. Eight premature infants above this weight responded well, averaging a drop of 42%. The smallest infants, however, uniformly responded to adrenocortical extracts, demonstrating the susceptibility of the eosinophils at this age to the action of the appropriate target-gland hormones. Jailer *et al.*[23] found an adequate response in 23 of 42 normal full-term infants from 4 to 24 hours of age. None of 23 premature infants were affected until the 9th day of post-natal life, at which time only 2 responded. The reaction was related to body weight and age in premature infants, an adequate response occurring at a later time in the smallest babies. All of 12 premature infants responded to ACTH. Jailer[22] has demonstrated experimentally that there is no response to epinephrin until the 8th day of life in newborn rats, or to physical stress until the 16th day. This was measured by the fall in ascorbic acid content of the adrenal cortex. They did, however, react to ACTH. He concludes that the adequacy of response to these agents is related to the maturity of the pituitary–adrenal axis. In the rat this maturity is not attained at full term, while in the human it may be, and is related to the degree of maturity at birth. The mechanism is not completely developed in premature (and some full-term) human infants, so that certain of the hazards of early life may be related to the inability to adjust to stressful situations.

Venning *et al.*[50] have, however, reported an elevated excretion of glucocorticoids in the urine of 2 premature infants exposed to stress (atelectasis). Jailer believes that such stress exceeds the stimulation by epinephrin.

The measurement of urinary steroids after the administration of ACTH to infants reveals, in general, a response increasing with age. Venning[47] found no rise in corticoids or 17-ketosteroids following the use of ACTH on the 2nd day of life. However, a significant elevation was seen on the 4th day with smaller doses. The minimal effective dose in the second week of life was 5 to 7 mg. Read *et al.*[35] found an increase of both steroids in the urine of newborn infants given ACTH, but the effect was greater in the second week of life. Klein[25] found the expected rise in these products in 12 newborn infants treated with ACTH. His report of a paradoxical increase in the urinary excretion of sodium with ACTH in the newborn infant has been detailed above. With continued administration of ACTH, Klein found an increased response over a period of days which

reached or exceeded adult levels. It is impossible to conclude that the improved response with time is due to increased maturity of the adrenal cortex, since, as Venning[47] has proposed, this may result from a "priming" effect of continued dosage on the adrenal cortex. Such an effect has also been seen in adults. Helper *et al.*[21] found increases in steroid excretion with ACTH in older children, comparable in degree to adult responses.

Conclusions. The singular hypertrophy of the fetal and newborn human adrenal gland and its rapid involution post-natally remain unexplained. The stimuli responsible for this phenomenon are unknown but it appears that the fetal hypophysis is essential to the initial hypertrophy[51]. The removal of the adrenal glands in fetal rats has not impaired development in any perceptible manner[46]. It is tempting to assign the responsibility for the higher excretion of 17-ketosteroids in the first days of life to the "fetal cortex", although extracts of this tissue have not shown androgenic activity. Other possible explanations for the early high levels have been presented. It seems unlikely that corticoids in the infant's urine arise from this portion of the gland, since their level rises during the first few days, when involution of the cortex is most rapid. The precise role or importance of the "fetal cortex", and the stimuli which induce its development, remain to be clarified.

The duality of the adrenal cortex in infancy and childhood is manifested by the variance in 17-ketosteroid and corticoid excretion in early life. The latter is excreted at a constant rate throughout life on the basis of surface area of the body, while the former remains low until puberty and the "adrenarche". It is possible that there are 2 independent endogenous adrenocorticotropic hormones[43], each stimulating different cells of the adrenal. One is secreted at a relatively constant rate throughout life, and the other becomes prominent at the "adrenarche".

Are the adrenal cortices of the infant hyperactive or hypoactive? The data relative to this question are conflicting. The balance of evidence is weighed against an insufficiency of the salt-retaining hormones in infancy. The low sodium and chloride concentrations of the urine cannot be applied to the question, because of inherent renal limitations in infancy which are probably beyond the reach of the adrenal cortex. It is recalled that potassium excretion is also low[53], a finding inconsistent with the known action of desoxycorticosterone. The low concentrations of sodium in the sweat and saliva of infants are more suggestive of adrenal hyperactivity, in the light of recent evidence that these indices are a sensitive reflection of this single adrenal hormone. The total base and chlorides of the blood of infants are equal to or higher than those of adults[18]. Jaudon's observations[24a,b] regarding physiologic hypoadrenal state are primarily clinical and may be confined to a circumscribed group of infants. The urinary excretion of corticoids in infancy has been shown to be adequate, and, within the limits of the method, may reflect, in part, the salt-retaining hormonal activity. However, more specific information, such as assay by the sensitive method using radioactive sodium[10a], is needed to solve this problem.

The comparatively high number of eosinophils in infancy intimate a lack of those steroids responsible for the production of eosinopenia. This possibility may be disclaimed by the specific measurements of Venning *et al.*[50], which reveal adequate quantities of glucogenic corticoids in newborn infants. The measurement of corticoids by chemical methods points to only a

slightly lower level in the first 3 days of life[34,48,50].

The relatively high excretion of 17-ketosteroids in the first day or two of life may be due to any of a number of factors previously discussed, and does not necessarily signify hyperadrenalism in infancy.

The response of the neonatal adrenal to adrenocorticotropic hormone is more marked in the second week of life than earlier. This may depend upon increasing maturity of the gland, but more likely denotes an improved reactivity with continuous administration due to a "priming" effect. Epinephrin, which stimulates the adrenal cortex indirectly via the pituitary–adrenal axis, produces a response which is related to maturity of the infant, body weight, and age. Likewise the effect of certain stresses, such as illness, in early life is dependent on these factors. The participation of the pituitary–adrenal axis in stressful situations is dependent upon these factors, more than the reactivity of the cortex to direct stimulation by ACTH. Thus, although there is no direct evidence to indicate, beyond doubt, a physiologic state of hypoadrenalism in the newborn infant, the pathways requisite to a full response to emergencies may be lacking.

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PROCEEDINGS OF

The Physiological Society of Philadelphia

SESSION OF NOVEMBER 20, 1951

Hormone Excretion in Patients with Liver Disease. F. C. Dohan, M.D., E. M. Richardson, Ph.D., L. W. Bluemle, Jr., M.D., and P. György, M.D. (Depts. Med. and Nutrit. Serv., Univ. of Penna., Phila.). There is considerable evidence to indicate abnormal metabolism of hormones in some patients with liver disease. In order to study the problem, the urinary excretion of the unconjugated and conjugated forms of the "estrone", "estradiol", and "estriol" fractions, as well as neutral 17-ketosteroids and gonadotrophins, have been determined for one or more periods in 5 normal men and 17 men with diffuse hepatic disease. The results are as follows: 1) Total estrogen excretion was increased in 11, and the unconjugated form in 6 of the patients. The group with most severe liver disease exhibited the highest excretion of both forms of estrogens. 2) The excretion of total estrogens showed a highly significant correlation with bromsulphalein retention and the total serum bilirubin values in patients with mild jaundice. Two patients with severe jaundice did not show increased estrogen excretion. There was no significant correlation with other tests of liver function. 3) The urinary excretion of total estrogens was significantly increased in the 4 patients with advancing or stable gynecomastia in comparison to that of patients with regressing or no gynecomastia. 4) High total estrogen excretion was associated with less than average gonadotrophin and 17-ketosteroid excretion. 5) Both forms of "estriol" were increased to a greater extent and more frequently than "estrone" or "estradiol". 6) The excretion of unconjugated "estriol" was significantly increased in the patients exhibiting stable or advancing cutaneous spider nevi. 7) The 17-ketosteroid excretion was less than normal in 14 of the 17 patients and was decreased in the 4 men with stable or advancing gynecomastia and the 6 men with loss of libido or testicular atrophy when compared to patients without these symptoms. 8) Gonadotrophins were significantly decreased in the 6 patients with testicular atrophy and/or complete loss of libido.

The results support the concept of disturbed hormone metabolism as a cause for some of the symptoms of diffuse hepatic disease and suggest that decreased biliary excretion of estrogens may, in part, be responsible for increased urinary excretion.

Measurement of Serum Cholinesterase Activity by a Photometric Indicator Method. J. G. Reinhold, Ph.D., L. G. Tourigny, B.S., and V. L. Yonan, B.A. (Pepper Lab. of Clin. Med., Hosp. of Univ. of Penna., Phila.). The method of Michel (*J. Lab. & Clin. Med.* **34**, 1564, 1949) has been modified so that change of pH caused by hydrolysis of acetylcholine chloride is measured by change in absorbency of phenol red indicator. The relationship between pH and absorbency is obtained by adding increasing amounts of 0.1 N HCl to the barbiturate-phosphate-sodium chloride buffer of Michel. Acetylcholine chloride, serum inactivated by heating 30 to 60 minutes at 60°C., and 0.01% phenol red solution are added and the absorbency is measured at

540 $\mu\mu$; pH plotted against absorbency gives a straight line between pH 7.1 and 8.0.

The amount of serum sufficient for a determination is 0.02 cc.; 0.1 cc. of serum is diluted to 10 cc. with the buffer and 2 cc. are placed in a cuvette; 0.2 cc. of phenol red and 0.2 cc. of acetylcholine chloride solution are added. The absorbency is measured in a photometer and the mixture then is incubated 60 min. at 25°C. A second reading is made and change in pH calculated. This technique gives results that average 0.03 unit lower than those by the original Michel method, a difference that can be disregarded for most purposes. The method was devised mainly to avoid the necessity for a pH meter but it has proved to be especially advantageous as a routine method and for carrying out determinations in large numbers. This method was used in testing 97 non-professional blood donors, found to be healthy by physical examination, who gave normal response when studied by means of sensitive liver function tests. The mean serum cholinesterase activity was 0.90 and the modal value 0.95; 98% of the activities were 0.60 or higher; only one exceeded 1.20.

Tissue Carbon Dioxide Tension During Oxygen Breathing at Pressures Greater than One Atmosphere. M. W. STROUD, 3RD, M.D., J. H. EWING, M.D., R. H. KOUGH, M.D., R. A. GOULD, M.D., and C. J. LAMBERTSEN, M.D. (Dept. of Pharmacol., Univ. of Penna.). At the January 1951 meeting of this Society we reported our inability to detect any but insignificant retention of carbon dioxide in normal men exposed to convulsant tensions of oxygen (3.5 atmospheres). These findings differ markedly from those reported from experiments on laboratory animals in which a large, early rise of carbon dioxide tension (pCO_2) in subcutaneous gas depots was found. Some investigators have felt that this pCO_2 rise was due to loss of the dual function of hemoglobin at such high tensions of oxygen and justified the belief that CO_2 retention in the brain played an important role in the etiology of the toxic symptoms of oxygen poisoning. For this reason, we undertook to carry out such experiments with refinements of technique suggested by our previous experience. When precautions were taken to insure the presence of complete equilibrium between the pCO_2 of the tissues and that in the bubble introduced to measure it, and when all gas samples were collected at the high pressure, we could demonstrate no rise in tissue pCO_2 in dogs breathing oxygen up to 6 hours at 4 atmospheres, or in men at 3½ atmospheres up to the onset of convulsions (as long as 90 min.). In rabbits breathing oxygen at 3½ to 4½ atmospheres also there was no rise in tissue pCO_2 until, at about 4 h., there was a sudden sharp rise coinciding with the onset of respiratory depression and convulsions. This delayed rise we regard as the result of an impairment in the pulmonary gas exchange which apparently does not occur in the dog or in man. We therefore reaffirm our earlier conclusion, that oxygen convulsions are not due primarily to the attainment of toxic pCO_2 levels in the brain.

Conversion of Hypoxanthine to Inosinic Acid by Pigeon Liver Enzymes. W. J. WILLIAMS, M.D., and J. M. BUCHANAN, Ph.D. (Dept. of Physiolog. Chem., Sch. of Med., Univ. of Penna.). Incubation of hypoxanthine labeled with radioactive carbon in the 4 position with pigeon liver extracts results in the formation of radioactive inosinic acid. It has been possible to precipitate the liver proteins containing the enzyme activity by adding ethanol to a concentration of 45% and lowering the temperature to —15°C. This pro-

cedure has made possible separation of the enzyme protein from cofactors and substrates which remain in the supernatant solution. In using the redissolved protein solution it has been found necessary to add adenosine triphosphate and ribose-5-phosphate to the incubation vessel in order to restore the enzyme activity. Further studies have indicated this activity is dependent on 2 (or more) enzymes. This may be shown by separating the pigeon liver protein into 2 fractions, 1 precipitating at an ethanol concentration between 0 and 15% and the other between 20 and 45%. By combining these 2 fractions, synthesis of inosinic acid can be obtained which is approximately twice the sum of the synthesis by the 2 fractions when these are incubated separately with the required substrates and cofactors.

BOOK REVIEWS AND NOTICES

ELECTROENCEPHALOGRAPHY IN CLINICAL PRACTICE. By ROBERT S. SCHWAB, M.D., Assoc. in Neurol., Harvard Med. Sch. Pp. 195; 106 ills. Philadelphia; W. B. Saunders Co., 1951. Price, $6.50.

DR. Schwab has fulfilled a long-standing need in electroencephalography by contributing a book which should be of great assistance to internists, neurologists, neurosurgeons, psychiatrists, and electroencephalogram technicians. It bridges a gap in clinical electroencephalography in that it is the only book available which is completely readable without a basic knowledge of electronics. It should prove extremely valuable as a reference, particularly concerning the clinical indications for the test (which still remains an expensive and time-consuming procedure). It is a valuable asset to the library of any hospital with electroencephalogram facilities. C. U.

CLINICAL PEDIATRIC UROLOGY. By MEREDITH CAMPBELL, M.S., M.D., F.A.C.S., Prof. Urol., New York Univ. Post Grad. Med. Sch., Visiting Urologist, Bellevue and Univ. Hospitals, New York. Pp. 1113; 543 ills. Philadelphia, W. B. Saunders Co., 1951. Price, $18.00.

THE author of this book on pediatric urology has had wide experience and is the recognized pioneer in this field of medical practice. The text of this book is presented in a concise but not dogmatic fashion. It is well organized. The paper is of good quality and the type is easily read. The illustrations are numerous and excellent.

Beginning with the chapter on "Methods of Examination and Diagnosis" the author continues in a logical manner with the symptomatology, diagnosis, and treatment of the urological diseases of infancy and childhood. The author has admirably stressed the importance of anomalies in the chapter "Embryology and Anomalies of the Urogenital Tract". This chapter is profusely illustrated. Practically every known anomaly is presented, together with a discussion of the symptoms, diagnosis, and treatment. Chapter 9, "The Adrenals", is a concise presentation of the numerous diseases affecting those organs. It should prove to be a welcome discussion to anyone interested in pediatric urology. The inclusion of the chapter, "Nephritis and Allied Diseases in Infancy and Childhood," is worthy of consideration. The material of the text of the chapter is accurate, informative, and well formulated and is a credit to the text as a whole.

The extensive bibliographical references and an excellent index add greatly to the value of the volume, in that they give a reliable and ready reference to so much authentic urological literature.

It is believed that this is the first concentrated attempt to embrace the entire field of pediatric urology in one volume. Although there are several points with which the reviewer is not totally in accord, this book is recommended to all physicians, urologists, surgeons or pediatricians interested in the practice of Pediatric Urology. L. M.

DIABETES CONTROL. By EDWARD L. BORTZ, M.D., Assoc. Prof., Grad. School of Med., Univ. of Penna. Pp. 264; 15 ills. Philadelphia: Lea & Febiger, 1951. Price, $3.50.

THE diabetic patient improves physically and psychologically in direct relationship to his metabolic control and understanding of the disease. This manual, compiled for diabetic patients, provides a thorough and simplified explanation of the many facets of this disorder which will aid in his education. An added advantage is a chapter supervised by Sister Maude Behrmann on meal planning based on Food Exchange Lists. Numerous recipes are included utilizing this method of diet preparation. C. S.

TEXTBOOK OF OBSTETRICS. By JOHN CUNNINGHAM, M.D., M.A.O., F.R.C.P.I., Prof., Obstet. and Gynec., Univ. Coll., Dublin, Ireland. Pp. 499; 297 ills. New York: Grune & Stratton, 1951. Price, $7.50.

THE most obvious single word which will describe this new textbook is "terse". It lacks the wordiness of many of our American textbooks without losing any of the meat of the subject in question. It is apparent that the author has utilized his wide experience and full knowledge of the subject in producing this excellent book. Its numerous illustrations complement the subject matter well. It will be most helpful to the student and the busy practitioner alike in finding quickly any subjects in question.

The chapters on Toxemias of Pregnancy and Hemorrhages of Pregnancy are particularly well done. As in most books by foreign authors, the drugs mentioned may be unknown to us, but their counterpart in our own therapeutic agents can be determined quickly.

C. M.

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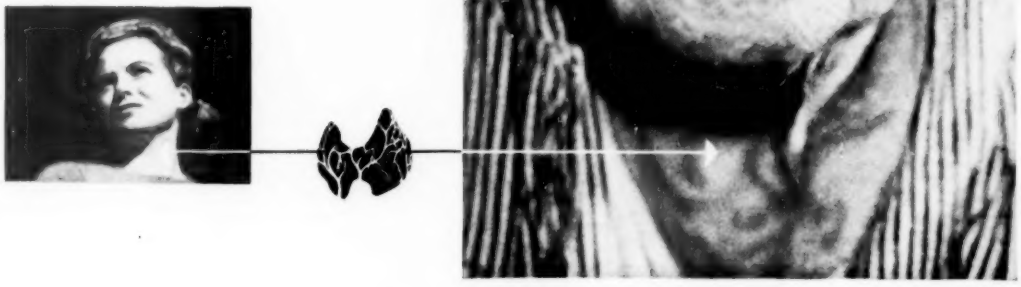

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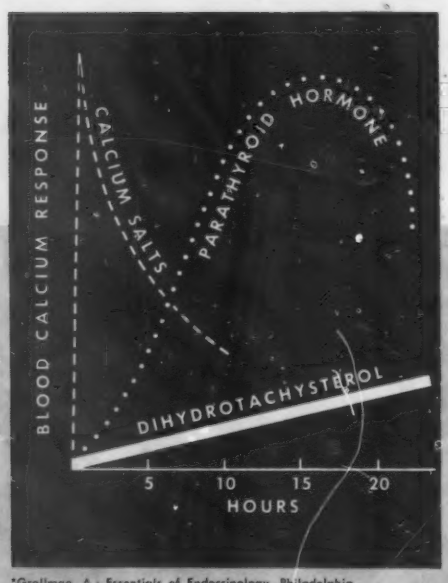

*Grollman, A.: Essentials of Endocrinology. Philadelphia, J. B. Lippincott Co., 1947, 2nd ed., p. 269.

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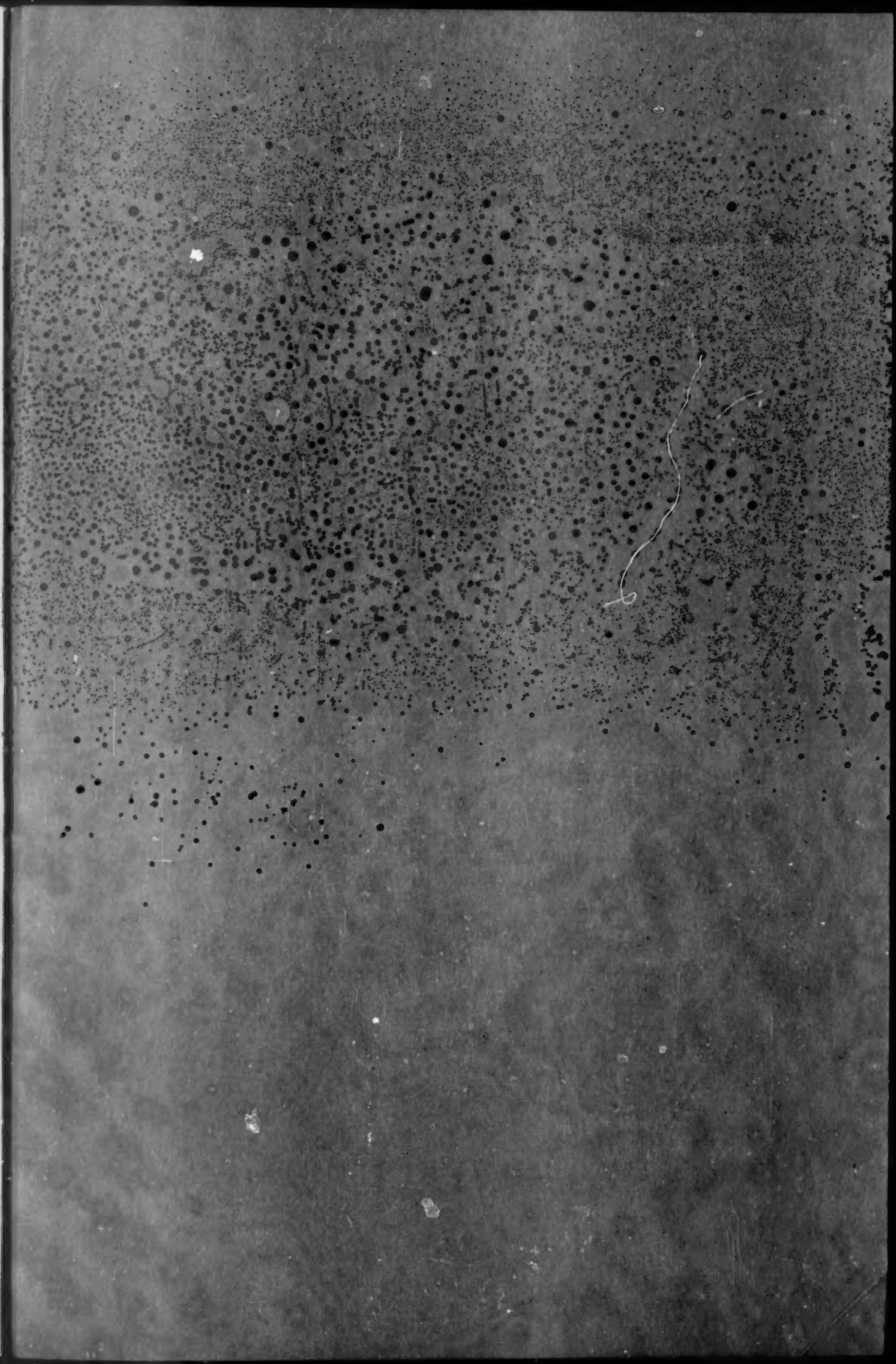
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